

TAG's Early Campaigns:

Reforming NIH AIDS Research, Boosting the Budget, and Revitalizing the Basic Science of HIV Infection

by Mark Harrington

On January 22, 2012, the Treatment Action Group marked its twentieth anniversary. Over the past two decades, we have helped to accelerate a historically unprecedented therapeutic revolution: the introduction of highly active antiretroviral therapy (HAART) in 1995-96, followed by its rollout to nearly seven million people worldwide. TAGline will publish a series of articles this year to examine the role of AIDS activism—and its evolving strategies—in these accomplishments, and how these experiences can help us build the long road towards the cure still ahead.

NOTE: For more in-depth coverage, including links to TAG's archive, please go online at: www.treatmentactiongroup.org/tagline/2012/Spring.

ACT UP's Legacy

TAG was formed by a group of activists from the AIDS Coalition to Unleash Power (ACT UP)/New York's Treatment and Data Committee (T+D), which had spearheaded ACT UP's work on accelerating HIV drug approval by the U.S. Food and Drug Administration (FDA), increasing community engagement

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What You Don't Know, You Can Sell:

Merck's Cavalier Attitude Towards the Welfare of HIV/HCV Coinfected Patients

by Tracy Swan

In places where access to antiretroviral therapy is widespread, people living with HIV are now dying from a common and curable coinfection: hepatitis C virus (HCV). HIV increases the risk for, and accelerates the rate of, liver disease from hepatitis C. Pegylated interferon and ribavirin, medications used to treat HCV, are less effective in people with HIV than in their HCV-monoinfected counterparts.

In 2011, the first hepatitis C protease inhibitors, Merck's boceprevir and Vertex's telaprevir, were approved based on trials in people with hepatitis C monoinfection. Both drugs are being studied in coinfecting people, thanks to pressure from the international HIV/HCV community and encouragement from regulatory agencies.

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The Odyssey of Therapeutic Vaccines for HIV

by Richard Jefferys

In the earliest days after the discovery of HIV in the mid-1980s, uncertainty reigned regarding how the immune system responded to the virus. Initially, it was thought that the time between HIV infection and the development of severe immunodeficiency and disease represented a period of viral inactivity or latency. In this context, it seemed logical to propose that perhaps vaccination could be used to bolster immune response to HIV and thus delay or even prevent the development of illness.

But the first efforts toward this goal quickly mired therapeutic vaccine research in controversy, casting an initial pall across the field that was compounded by the failure of any candidate to show significant efficacy. Additionally, the scientific rationale for the approach evolved as more was learned about the pathogenesis of HIV infection and the types of immune responses that may be effective—and ineffective—at controlling the virus. After a period in which enthusiasm regarding the prospects for therapeutic vaccines waned, the recent resurgence in interest in research aiming to cure HIV infection has offered new reasons to pursue their development.

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in clinical trials conducted by the National Institutes of Health (NIH), fighting industry to bring down high drug prices, and demanding innovative expanded-access programs for people with AIDS unable to enter clinical trials of lifesaving experimental drugs.

ACT UP had won significant concessions from the FDA, leading to parallel track in 1989 and accelerated approval in early 1992, and from the NIH, leading to the formation of the Community Constituency Group (CCG) in 1990 and to activists and persons with AIDS being represented on all research committees of the AIDS Clinical Trials Group (ACTG) and other NIH AIDS research networks. By 1992, two drugs were approved to treat HIV and a handful more were approved to treat or prevent the most common opportunistic infections.

Despite these early victories, effective combination therapy was still years away. The death toll kept rising, seemingly impervious to the interventions of ACT UP and other activists, as well as those of the research establishment. There was no national strategy to deal with AIDS, and no national research plan. For twelve long years, the Reagan and first Bush administrations had turned a deaf ear to the enormity of the AIDS crisis. Congress (then led by Democrats in both houses) had taken halting legislative action at several points, funneling money to the NIH for AIDS research, as well as creating a weak coordinating entity at the NIH to help its many institutes. In 1990, Congress had passed the Ryan White CARE Act, which created a funding mechanism to pay for expensive AIDS treatments, though there were as yet insufficient drugs to make a dent in the epidemic's deadly swath.

Within ACT UP, disagreements about strategy, tactics, and targets were inflamed by the desperation all around us. With the promise of new drug classes in the pipeline and proof-of-concept combination

treatment still in clinical trials, TAG's founders believed that the solutions and ultimately the end of the HIV pandemic would come from more—not less—community engagement with research to accelerate the development of better treatments, a cure, and a vaccine. It would require a dedicated cadre of treatment activists working full-time with organizational support. It was clear that we were in it for the long haul.

How to Survive a Plague
(www.howtosurviveaplague.com),
a new documentary by David France
covering those early years will be in
theaters this fall.

Spurred by the changing environment and the upcoming presidential and congressional elections in 1992, TAG decided to try out a think-tank approach to changing the nation's response to AIDS. Frustrated by three years of activist experience inside the ACTG—which spent only one-eighth of the \$800 million Congress was appropriating for AIDS research by 1992—TAG pursued two initial strategies to address the apparently unstoppable pandemic. The first was to rectify institutional failures at the NIH by examining its research investment in detail and proposing more effective ways to ensure progress. The second was to advocate for moving beyond drug development and clinical trials to the basic science, where the still critically unanswered questions of how HIV destroyed the immune system could, if unlocked, pave the way to better therapies, and—it was hoped—eventually a cure and a vaccine.

I. Reforming the NIH AIDS Research Program

First, TAG decided to deconstruct the entire AIDS research program at the NIH and to recommend reforms to ensure that all critical scientific questions were addressed. Just as ACT UP's Treatment and Data Committee in its 1989 *Critique of the AIDS Clinical Trials Group* had examined what studies were being

done, who was leading them, who sat on the key committees, and who controlled the money, so in 1992 TAG's Gregg Gonsalves and I undertook a comprehensive examination of the NIH AIDS research program.

To do so, we went to the NIH campus in Bethesda, Maryland, and met with the staff of the weak and underfunded Office of AIDS Research (OAR), whose director was Anthony S. Fauci. Fauci was also the director of the largest NIH recipient of AIDS research dollars, the National Institute of Allergy and Infectious Diseases (NIAID). This created an obvious conflict of interest as well as a disincentive for OAR to probe too deeply into the spending decisions of other institutes, since it would seem to be one institute director criticizing his peers. We met with OAR deputy director Jack Whitescarver and his indomitable senior advisor Wendy Wertheimer. They provided us with valuable information about the OAR and its workings, and gave us key contacts at all the institutes. Gregg and I spent several months plowing through crates of documents sent to us by OAR, NIAID, and the other institutes. We read every NIH-funded AIDS research grant as well as the program descriptions supplied by the institutes.

TAG's NIH report came out at the Amsterdam AIDS conference in July 1992; the conference had been moved from its original site, Boston, because of George H. W. Bush's ban on HIV-positive immigrants and tourists from visiting the United States.

We presented our findings at a press conference in Amsterdam on July 22, 1992. In attendance along with the press was Patsy Fleming, an AIDS advisor to New York Congressman Ted Weiss. Less than six months later after the election of Bill Clinton as president, new Health and Human Services Secretary Donna Shalala appointed Fleming as a senior advisor, a role that enabled her to push for TAG's recommended reforms inside the new administration.

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Throughout 1992, a wave of activist colleagues from ACT UP and TAG died of AIDS, including ACT UP/San Francisco's Michael Wright in January, TAG's Scott Slutsky in May, artist/writer David Wojnarowicz in July, and ACT UP/New York's Mark Fisher just before the November elections. When we marched uptown on election eve, 1992, bearing Mark's body to Bush's New York City campaign headquarters in midtown, most of us felt that it would be only a matter of time—and not much time—before we too died of AIDS. But we were determined to push for changes in the research system so that later generations of the infected would have a better prognosis and a chance for a longer life.

The NIH Revitalization Act of 1993

Clinton's victory opened up a new path for NIH reform. President Bush had been holding back an overdue legislative renewal of NIH's mandate due to concerns about fetal tissue research—which were to recur a decade later early in his son's administration with stem cells. Congressional leaders were determined that the NIH reauthorization should be one of the first bills to move in the new Congress. Indeed, Senator Edward Kennedy introduced the NIH Revitalization Act of 1993 as Senate bill 1 on January 21, 1993, just one day after Clinton's inauguration. The bill included all of TAG's recommendations from the July 1992 report in its title XXIII, which would lead to a sweeping reorganization of AIDS research at the NIH, the departure of Fauci from his post as head of OAR, and a long-overdue external scientific review of the whole program.

Despite opposition mobilized by Fauci and the other institute directors, who disliked the NIH Reauthorization Act's removal of their authority over AIDS research spending decisions to OAR, the bill passed in the Senate by a bipartisan supermajority (the bill was cosponsored by Kansas Republican Senator Nancy Kassebaum, one of a number of then-dwindling, now virtually extinct, moderate Repub-

AIDS Research at the NIH: A Critical Review (1992)

Our goal was to obtain a comprehensive picture of the AIDS programs administered by the US NIH in order to recommend changes to expedite a cure. We reviewed the \$800M NIH AIDS program from fiscal year (FY) 1991, including 2,625 extramural grants and contracts and hundreds of intramural projects....NIH spent \$800M on AIDS in FY 1991, 9.7% of its total budget. Each of the NIH's [then] 18 Institutes, Centers, and Divisions administers AIDS programs, all of which remain un-coordinated and underfunded....Under the President's FY93 Budget Request, AIDS programs will increase only 3.8%, or less than scientific inflation. This is a cut of \$45M from the institute directors' original requests. Over a hundred new initiatives and expansions of existing programs cannot be funded....The NIAID pool of basic AIDS research grants shrank by half in 1992....

We conclude that the entire NIH budget should be doubled to \$16 billion a year. The AIDS budget should rise to \$1.6 billion. The rate at which AIDS basic research grants are funded should be restored to 40%. The NIH Associate Director for AIDS Research [the OAR Director] should be given authority to allocate resources and programs across institute boundaries. Pathogenesis research should be emphasized. [Abstract, *AIDS Research at the NIH: A Critical Review*. Gregg Gonsalves and Mark Harrington, TAG, July 1992.]

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licans in Congress). In the House, Fauci's allies had time to mobilize. A number of professional societies testified against the bill. On the side of reform were Art Ammann and Elizabeth Glaser of the Pediatric AIDS Foundation, Mathilde Krim of amfAR, and David Ho of New York's new Aaron Diamond AIDS Research Center. The House passed the bill on a party-line vote, and President Clinton signed it in the Rose Garden on June 10, while TAG was in despair at the early results of combination HIV treatment studies at the International AIDS Conference in Berlin.

Bill Paul as OAR Director and the Levine Committee Report

In August 1993, Clinton named Nobel Prize-winning virologist Harold Varmus as the new NIH director. In turn, Varmus named NIAID immunologist William E. Paul—a legendary basic scientist and author of the leading immunology textbook—as the new OAR director in February 1994. Following TAG's recommendations

from 1992, Paul convened a blue-ribbon panel—dubbed the Levine Committee after its chair, virologist Arnold Levine from Rockefeller University—to conduct an extensive external review of the entire NIH AIDS research effort. Numerous TAG members and other activists participated in this review, which issued its final report in 1996. The report recommended 14 top priorities for NIH AIDS research, including the formation of an NIH Vaccine Research Center (VRC), coordination of clinical trials, and the prioritization of basic science and pathogenesis research.

II. Back to Basics: Revitalizing Basic Research on AIDS

Just as TAG's early examination of the failures of the institutional structure at the NIH led to reforms there in the following decade, so TAG's early emphasis on revitalizing basic science led to a surge in research to reveal how HIV causes disease, or pathogenesis.

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This work began with T & D in the early 1990s when Gregg Gonsalves, who had recently left Tufts University and was working in Columbia University's famous Morgan genetics laboratory, proposed that the NIH hold a series of meetings on why certain people seemed to be protected from HIV infection despite repeated exposures (the so-called exposed uninfecteds), while others seemed to progress much more slowly to full-blown AIDS (the so-called long-term non-progressors, later dubbed elite controllers). This led to a series of scientific investigations in these unusual people who had some biological ability to resist HIV infection or disease progression.

Pathogenesis + Activism (1992)

In 1992 at the Amsterdam AIDS conference, alongside the presentation of TAG's recommendations for NIH reform, I gave a talk, "Pathogenesis + Activism," laying out the urgent necessity of activist and scientific attention to the unsolved questions of how HIV caused disease. It was still thought in the early 1990s that HIV lay dormant in some unknown parts of the body, before becoming reactivated and causing progressive immunodeficiency. Fauci had spoken of this unsolved medical mystery issue at the 1991 AIDS Conference in Florence.

In April 1992, I met with gastroenterologist Don Kotler at St. Luke's-Roosevelt Hospital in New York, and underwent a lymph-node biopsy. Immunologist Giuseppe Panteleo, then at Fauci's NIH lab, put it on ice and flew it to the NIH where Fauci, Jan Orenstein, and colleagues could examine my immune-system tissue to find out more about where HIV was hiding and replicating, and how it was damaging the body.

In Amsterdam I showed giant slides of the lymph-node biopsy to the International AIDS Conference audience, and described the uncanny and frightening feeling of being infected with a pathogen whose damage was

devastating yet often for many years clinically silent. The slides showed an outwardly healthy lymph node (my CD4 count was 660 cells/mm³, and viral-load tests were in their infancy), but on closer examination, when stained with a dye that bound to HIV, they showed that—in Don Kotler's inimitable phrase—my lymph nodes were "crammed with virus." More magnified images, which looked like galaxies of stars in formation, showed singly infected cells producing a series of greenish viral particles.

Just as Peter Staley at the San Francisco AIDS Conference in 1990 inaugurated a new era in activist-scientist relations by calling for scientists and activists to work together—just two months after ACT UP's "Storm the NIH" demonstration at the NIH campus in Bethesda—so in Amsterdam I called for activists to work not only with clinical but with basic science researchers to unlock the mysteries of AIDS. I called for a revitalization of basic science, more funding, better communication between activists and basic scientists, and for basic science to use clinical samples from actual patients rather than the more artificial laboratory-adapted strains then in common use.

The Basic Science of HIV Infection: A Report from the Front (1993)

In spring 1993, while Congress was still debating the fate of the Office of AIDS Research, Gregg Gonsalves set out on a nationwide tour to interview some 36 leading AIDS researchers to better understand the issues they were facing and what they needed to make progress. Gregg's report, *The Basic Science of HIV Infection: A Report from the Front*, presented at the grim Berlin AIDS Conference where the failed results of so many combination therapy trials pushed the field towards despair, laid out a number of ways to improve AIDS research by making it more relevant to the people with the disease and not limiting it just to artificial laboratory viral strains and immune cells. He

called on researchers urgently to investigate the so-called correlates of protective immunity to HIV, to examine the interaction of the virus in the living, complete host ("in vivo veritas"), to better understand HIV pathology in vivo, and to better understand the viral life cycle. He described the still-harsh conditions facing new researchers with the legacy of the Reagan-Bush funding crunch at the NIH and proposed incentives to bring new researchers and experts from other fields into AIDS research. Gonsalves's 1993 report still reads like a clarion call for what is needed to scientifically understand, defeat, and ultimately eradicate HIV.

Clinton Administration Funding Increases Surge in Basic HIV Science

Hand in hand with the OAR legislation, the Levine Committee report, and the reforms that resulted came a doubling of the NIH AIDS research budget in the first Clinton administration. In the second, Clinton and Congress agreed to double the NIH budget as a whole. Thus, from 1992 to 2002, the AIDS research budget at the NIH rose from \$800 million to \$2.4 billion. In 2012, it is about \$3.1 billion, or 10% of NIH's \$31 billion.

The OAR campaign led to a massive reinvestment in basic science, drawing a new generation of scientists into AIDS research. The NIH founded the Vaccine Research Center in the wake of the Levine Committee report. Other changes were harder to obtain, such as the coordination of clinical trials across multiple institute lines. In the end, Fauci and the institute directors gained from the OAR legislation as it helped sharpen the focus of each institute on what it did best.

Results of the Campaign

Among the most exciting results of the new investment in basic science were the discovery in 1995-96 by several labs at the National Cancer

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Institute (NCI), NIAID, and Aaron Diamond, of the two cellular coreceptors that HIV uses to get into cells—the CXCR4 (or X4) and CCR5 (or R5) receptors. Besides unlocking the cell to HIV along with its first receptor, CD4, these two molecules also unlocked a whole series of scientific mysteries long noted in the literature, such as why certain strains of HIV preferred to infect CD4 T cells while others infected macrophages, and led to the discovery and development of a whole new class of anti-HIV drugs, the CCR5 receptor blockers, the first to be approved of which was Pfizer's maraviroc (Selzentry) in 2007. The identification of CCR5 also provided the basic-science rationale for the bone-marrow transplant therapy in Timothy Brown, the only person to be cured of HIV infection to date.

These are some of the results of TAG's first years of activist efforts to reform AIDS research at the NIH, massively increase research funding, and turn the field back to fundamental basic science to better understand, so as to better control, how HIV causes disease.

Two decades later, treatments continue to improve, saving and prolonging the lives of millions of people around the world, preventing countless new infections, and bringing hope that the single documented case of an HIV cure can be replicated, while the ultimate objective of a cheap and widely accessible cure and vaccine remains elusive.

Despite the advent of HAART and its global rollout, we are far from the end of the pandemic. The same combination of smart advocacy, good science, and more money, which helped lead to the HAART breakthrough in the mid-1990s, is now needed to revitalize political leadership, increase research funding, and encourage a new generation of scientists to embark on the search for a cure and a vaccine, the two prerequisites for ending AIDS once and for all.

The same combination of smart advocacy, good science, and more money...is now needed for a cure and a vaccine.

Just as in 1992, the current political situation is dire. Last year only 10% of all NIH grants submitted were funded—meaning 90% of them were rejected. This is bad news for young scientists, some of whom are likely to leave research altogether. While last year President Obama called science and technology growth essential to America's future, this year he recommended a flat NIH budget for fiscal year 2013—a far cry from his original (2008) campaign promise to ensure that NIH funding would be doubled over the current decade. TAG recommends that the NIH as a whole, along with the AIDS research budget organized by OAR, increase by 15% per year, which would allow a doubling by 2020.

Similarly, while therapy continues to improve, scientists are at an impasse with efforts to discover a cure and a vaccine. High-risk and innovative science driven by a comprehensive and coordinated research agenda will be essential to making these goals into realities. Many of the tenets of Gonsalves's 1993 report remain central to AIDS research today—as NIAID acknowledged in its recent funding opportunity announcement (FOA), "Targeting Persistent HIV Reservoirs (TaPHIR)," which is designed "to stimulate the development of innovative tools and strategies for curing HIV infection....Novel approaches are therefore sought to efficiently monitor and specifically target reservoirs of latently infected cells to facilitate the testing of strategies to cure HIV infection in vivo." The FOA specifically requires that "latently infected reservoir cells from HIV-positive individuals on optimized HAART should be used for validation studies whenever possible." (grants.nih.gov/grants/guide-pa-files/PAR-12-109.html.)

In addition, the FDA needs to be brought in early to participate in

the discussions about how to optimally conduct cure-related clinical trials to ensure the proper balance of rigor, flexibility, ethics, safety, and ability to answer the questions. In 2011 TAG, along with amfAR, AIDS Policy Project, and Project Inform, held an international consultation to discuss how to advance this work. Recently, the FDA and NIH commissioned a high-level scientific working group to address these issues over the coming 18 months, to be coordinated by the Forum for Collaborative HIV Research.

Finally, the struggle for domestic and global treatment access remains daunting. In the United States, almost 4,000 people are on AIDS Drug Assistance Programs (ADAPs) waiting lists, and globally 8 to 10 million people will need antiretroviral therapy in the coming two years, while funding by the U.S. and others is being cut.

AIDS has not yet emerged as an issue in this presidential campaign. It needs to if we are to successfully engage the national leadership in the demanding the necessary work ahead to end AIDS.

In coming articles we will examine the serial disappointments of early combination-therapy trials in the early 1990s, the crisis of confidence that led TAG to call for more rigorous and longer-term trials to better define the clinical utility of the next generation of HIV drugs—the protease inhibitors—as well as TAG's work on HIV-associated opportunistic infections and cancers, and the unexpectedly electrifying, medically revolutionary results of the combination of triple antiretroviral therapy, the clinical use of quantitative viral-load tests, and the advent of HAART in 1996, whose use is still being refined, optimized, and in the meantime rolled out to almost seven million people around the world. •

Does Obama's 2013 Budget Herald the End of PEPFAR?

Devastating Funding Proposal Undermines the Global Fight Against AIDS

by Coco Jervis

A sense of disbelief washed over the global AIDS community last month when President Obama unveiled his fiscal year 2013 budget proposal to cut \$563 million from the President's Emergency Plan for AIDS Relief (PEPFAR) program. Cuts of this magnitude could lead to half a million people being denied lifesaving treatment, and countless preventable new infections. Shock and dismay have since given way to frustration; some feel the administration is signaling that an era of U.S. leadership in the global fight against AIDS may be coming to an end.

Since 2003, PEPFAR has been the most efficient and effective global health program in U.S. history. At its outset, millions of people living in sub-Saharan Africa and other low- and middle-income countries were dying of HIV without any hope of access to lifesaving antiretrovirals (ARVs). Entire communities were ravaged by disease, a generation of children was orphaned, and funeral homes could not keep up with demand. The vigilant work of activists brought these images and stories of horrendously suffering people to the world's attention. When President George W. Bush decided to make the global fight against AIDS an administration priority during his first term in office, PEPFAR was welcomed with unparalleled public and bipartisan congressional support.

By the end of President Bush's tenure, PEPFAR was arguably his administration's only foreign policy success. Two million men, women, and children had been put on treatment, over a million lives had been saved, untold numbers of new infections had been averted, and a quarter of a million children had been born free of HIV. Although the program was not without its flaws, the public and Congress were proud of the achievements made by PEPFAR and felt committed to build on its successes.

In 2008, the program was reauthorized for five more years, again with bipartisan support.

When President Obama came into office, one of the first things he did was appoint Dr. Ezekiel Emanuel, a bioethicist at the National Institutes of Health (NIH), as chief special adviser on health issues. Soon after, an internal discussion was advanced about the future direction of U.S. global health programming. The question posed was: How could the Obama presidency make its own mark on global health and differentiate itself from its predecessor's successes? Less than a year later, in May of 2009, President Obama announced the creation of the Global Health Initiative (GHI), a comprehensive realignment of U.S. global health aid and development strategy. The aim of GHI was not necessarily to strengthen or build on PEPFAR, but rather to "broaden the U.S.'s involvement in global health." In other words, the administration decided it was time to move away from the fight against AIDS and to invest in other global health diseases that could be fought, prevented, or eradicated at a lower cost. Following the launch of GHI, the Obama administration began distancing itself from PEPFAR by referring to the fight against AIDS as a "shared responsibility" and by insisting that the program needed to focus on "greater efficiencies."

Some efficiencies—such as the promotion of comprehensive sex education, the removal of the global ban on syringe-exchange funding, better integration of TB/HIV services, and a refocusing of efforts on marginalized groups—were obviously needed and long overdue. However, one critical efficiency—drug pricing—that the administration has more control over than it would like to believe, could in fact be the biggest factor in the perceived lack of shared responsibility by low-income governments. For over a decade now, AIDS activists

have been fighting the impact that intellectual-patent barriers have on access to essential medicines. At times, the administration's own trade policy has undermined its purported goal of greater cost efficiencies. Government officials, civil-society organizations, and clinicians from Thailand, Brazil, India, and Ecuador to name a few, have lamented how U.S. trade policy has interfered with their ability to define patent criteria and to issue compulsory licenses to reduce the cost of lifesaving ARVs for their own people.

Over 34 million people worldwide have HIV, of whom 30 million are living in low- and middle-income countries. According to the most recent World Health Organization and UNAIDS estimates, at least 15 million people need treatment now, but only 6.6 million currently have access—the vast majority provided by PEPFAR and/or the Global Fund.

Founded in 2002, the Global Fund is the world's largest multilateral donor for AIDS, TB, and malaria programs. The Fund is a public-private partnership, supported by multiyear commitments made by G20 and individual philanthropic donors. Due to the global economic crisis, the Global Fund faced a multibillion-dollar gap, and was unable to fully fund some of the proposals submitted last year by organizations and countries with large epidemics to support their prevention, treatment, and care efforts. The lack of funding commitment also led to the cancellation of the latest round of grants. The organization is now trying to recover after the U.S. banded together with other donors to force the exit of its distinguished executive director, Dr. Michel Kazatchkine, only to have him replaced by an untested and inexperienced retired banker with no experience in global health.

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While the Global Fund has had its share of problems, it is addressing them with transparency and commitment. Without full backing by the U.S. and other donor nations, countless lives will be lost. We have already heard of HIV programs not having enough money to enroll new patients who urgently require ARVs and existing patients forced into treatment interruptions. Progress to increase the numbers of people tested for HIV is being threatened because people are hearing that treatment is not available, and the newly diagnosed or newly ill have no place to receive appropriate care.

While administration officials may claim that the proposed half billion dollar cut to PEPFAR will be partly offset by a proposed increase in U.S. support to the Global Fund, what is really happening is a robbing of Peter to pay Paul, as PEPFAR and the Global Fund complement each other, and fully funding each of them is essential to achieving universal access to prevention, treatment, and care.

Battered by the persistent economic crisis, faltering commitment by donors, and changing fashions in global health, the collective global fight against AIDS is wavering. The Obama administration, while long on promises, has routinely come up short on performance. Evidence of impact or even metrics of measurability for the GHI, or the U.S. National AIDS Strategy for that matter, remain elusive.

This past December, on World AIDS Day, the world commemorated 30 years of fighting the epidemic; the administration responded by launching more new initiatives. One is to increase the PEPFAR target to reach a total of 6 million people on ARVs by 2013, and the second is to globally eradicate pediatric HIV by 2015. Both of these goals are laudable, and the administration's announcement was met with much fanfare. Yet in a stunning reversal (or, some may argue, sleight of hand) not three months after making these new commitments, the administration proposed

...in a stunning reversal, or some may argue, sleight of hand...the administration proposed a drastic and ominous cut one year before PEPFAR's reauthorization.

a \$563 million cut for next year's PEPFAR budget—a drastic and ominous cut to make one year before the program's congressional authorization will need to be renewed.

So we are left with the reality that gone seems to be the commitment by the administration to fight AIDS; gone seems to be the enthusiasm and political will by the G20 to achieve universal access; gone—by attrition or retirement—are most of the champions of PEPFAR who roamed the congressional halls drumming up support for the program in 2003 and 2008. With the administration's commitment to a third reauthorization of PEPFAR in jeopardy, and many of the Global Fund donors fleeing for the exits, the stage is being set for a global health catastrophe.

Portents of doom aside, there remains a real question about the future of U.S. leadership in the global fight against HIV. Take, for instance, Obama's proposed zero-sum increase of next year's NIH budget, despite his campaign promise before the 2008 election to double that budget over the coming decade. The president is way off track in meeting his promise, which is consequently undermining our ability to translate scientific advances into cures, jeopardizing our nation's long-term status as the global leader in health research, and turning back the clock on the search for an AIDS cure and better treatments for hepatitis C and TB. Further, with looming threats of sequestration ahead—which could lead to a 9% across-the-board cut for the NIH—and the growing inflationary burden of research and development activities, flatlining the NIH budget is, in real terms, a cut.

NIH-funded biomedical research has recently led to a number of break-

throughs, not only with microbicides and medical male circumcision, but also with the recent finding that anti-retroviral treatment reduces the risk of HIV transmission by 96%. These biomedical advances suggest that by scaling up people on treatment we can turn the tide on the global epidemic. However, in order to do so we must continue to translate the science into applicable interventions, which will require more research, the best and brightest scientific minds, and a long-term robust commitment to funding the NIH.

Finally, negligible increases in Obama's 2013 budget for the Centers for Disease Control and Prevention's (CDC) work to fight the two leading killers of people with HIV—TB and hepatitis C—as well as continued insufficient attention to the National HIV/AIDS Strategy and a worsening domestic AIDS crisis in marginalized populations demonstrate that the administration's wavering commitment in the fight against HIV does indeed cut across geographical lines. Increasing division between the domestic and global epidemics in the U.S.-based AIDS advocacy community needs to be reexamined as we fight harder and harder each year for increasingly inadequate pots of funding.

Make no mistake—reduced spending in the short term will affect progress in the fight against HIV/AIDS in the long term. As we move forward in this election year and continue to educate political leadership, we must remind them what is truly at stake. We must demand less rhetoric and more action, unity for fighting both the global and domestic epidemics, and bolder asks that belie the reality that we are on the front lines of making the invisible visible—the suffering of millions of people living with HIV/AIDS in the U.S. and around the world. •

The Odyssey of Therapeutic Vaccines for HIV

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History

The controversy that attended the earliest research into therapeutic vaccination began in the mid-1980s when a French scientist named Daniel Zagury obtained a vaccinia virus from the National Institutes of Health that had been modified to include several components from HIV, and proceeded to test it in both HIV-infected and -uninfected individuals in Paris and Zaire without appropriate regulatory approval (the vaccinia construct had been created only for the purpose of conducting studies in animals). Several of the HIV-infected participants died, and this fact was omitted from published reports about the experiments (which instead attempted to suggest the vaccine was efficacious).

Following quickly on the heels of this debacle were two more woeful contretemps relating to therapeutic HIV vaccine candidates. A company named MicroGeneSys created a vaccine containing the HIV gp160 protein, and Robert Redfield, a scientist with the Walter Reed Army Institute of Research, conducted trials in people with HIV. At the International AIDS Conference in Amsterdam in 1992, Redfield claimed the preliminary results were encouraging but quickly came under fire for overstating the findings. The situation was aggravated by a successful attempt to secure a \$20 million congressional appropriation specifically to conduct an efficacy trial of the vaccine, bypassing normal research review mechanisms (this money was ultimately redirected after Redfield's initial analysis was shown to be unreliable).

The International AIDS Conference in Berlin in 1993 was the site of the third blow to the credibility of therapeutic HIV vaccine research. A great deal of enthusiasm had attended Jonas Salk's venture into the field in the late 1980s, when he described the development of a vaccine comprising

a whole-killed HIV isolate that was intended to be tested as a preventive and therapeutic vaccine. Due to regulatory concerns about the safety of killed vaccines in HIV-negative individuals, Salk focused on therapeutic studies. Results were hotly anticipated and due to be presented in Berlin, but they were not debuted at the conference itself, but rather at a news conference; this decision fostered distrust and anger among attendees before the data were even described. The unimpressive outcomes of the trials, which Salk and the Immune Response Corporation (the company set up to produce the vaccine) tried to spin positively, served as the final insult.

As these disasters piled up, scientific advances were also undermining the original rationale for the approach. The notion that HIV was latent during the asymptomatic phase of the infection was overturned by data showing that the virus was constantly replicating, and that this replication was accompanied by the ongoing proliferation and death of CD4 T cells. Improvements in tools for evaluating immune responses revealed that there is a massive specific response to HIV that, in most individuals, is unable to control viral replication, leading to a situation where the immune system essentially flails away at the virus throughout the course of infection. Furthermore, CD4 T cells responding to HIV (HIV-specific CD4 T cells) were shown to be preferentially infected, contributing to their poor functionality and inability to deliver appropriate help to the other vital components of an antiviral immune response: CD8 T cells, whose primary task is to recognize and kill virus-infected cells, and B cells, which generate antibodies that—when effective—glom onto free floating viral particles and prevent them infecting new cells. These findings seriously called into question the idea that adding more HIV antigens into the mix via therapeutic vaccination—

when the virus itself was failing to induce protective immunity—would be beneficial. While research did not entirely come to a halt, it was not viewed as a priority, and hopes for a successful therapeutic vaccine faded.

A Second Try

The burgeoning success of triple combinations of antiretroviral drugs (ART) in the mid-1990s might have been expected to further erode interest in therapeutic vaccines, but it ultimately led to a mild revival in interest, for two main reasons. Firstly, the drugs were clearly imperfect in terms of safety and side effects, leading to interest in approaches that might allow intermittent or delayed use of ART. Secondly, the profound suppression of HIV replication mediated by ART facilitated reconstitution of the immune system, and some scientists speculated that this may offer an opportunity to use vaccines to induce new HIV-specific immune responses that could develop (or “mature” in vaccine parlance) without interference from HIV because the drugs were keeping the virus at bay.

These ideas prompted a slew of new trials combining a variety of vaccine candidates with ART. These candidates included Salk's whole-killed vaccine (now called Remune), attenuated viruses used as vectors to deliver HIV antigens (such as the canarypox-based ALVAC and cowpox-based MVA), and “naked DNA” constructs that deliver the genetic code for making vaccine antigens into cells. Data were generated showing that HIV-specific CD4 and CD8 T-cell responses could be induced in individuals with suppressed viral loads, and in some cases laboratory tests suggested that the functionality of these T-cell responses was markedly superior to those present prior to vaccination. But the harder question to answer was whether these apparent immunologic effects of therapeutic vaccines could be translated into a measurable health benefit.

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Remune underwent testing in a large, randomized, placebo-controlled phase III trial that evaluated whether vaccination reduced morbidity and mortality in people with HIV, the vast majority of whom were on ART. No significant differences in the incidence of opportunistic infections or deaths were seen, but the interpretation of the results was complicated by the fact that the standard of care for ART evolved from dual- to triple therapy while the trial was ongoing, and that there were—happily—very few endpoints in both the Remune and placebo arms. Because the effectiveness of ART made it essentially impossible to demonstrate an additional benefit from therapeutic vaccination, alternative study designs became more common. There were two main approaches. The first was to immunize individuals on ART and then evaluate the effects on CD4 T-cell levels and viral load during an ART interruption (in hopes of allowing extended breaks from ART). The second was to administer therapeutic vaccines to individuals with early infection prior to ART initiation (in hopes of being able to show a delay in reaching CD4 thresholds indicating a need for ART). Data from these types of trials occasionally hinted that receipt of therapeutic vaccines was associated with better preservation of CD4 T-cell counts and slightly lower viral loads during ART interruptions, although at least one trial of ALVAC showed the opposite. A still-unpublished South African trial of a DNA vaccine suggested that it might have slightly delayed CD4 T-cell declines and the associated indication for ART.

New Dawn Fades

Once again, however, scientific advances served to undermine the rationale behind these studies. Specifically, the idea that ART could be safely interrupted as long as CD4 T-cell counts were maintained was shown to be erroneous by the sobering results of the Strategic Management of Antiretroviral Therapy (SMART) trial. SMART had the

specific goal of assessing whether intermittent, CD4-guided ART could be as effective as continuous ART, but the trial had to be stopped early because individuals in the intermittent arm experienced a doubling in risk of illness and death. Analyses demonstrated that these events were associated with inflammation resulting from unsuppressed viral load, prompting additional investigations into the link between inflammatory markers, uncontrolled HIV replication, and health outcomes. This type of research has now been conducted in multiple cohorts in diverse global settings, and it has reinforced the conclusions from SMART: inflammatory markers are linked to viral load and show significant associations with morbidity and mortality; measures of cumulative exposure to viral load prior to ART initiation have also been shown to be associated with risk of morbidity and mortality after starting ART.

The window of opportunity for therapeutic HIV vaccines therefore narrowed once more, as it was clear that slight diminutions in viral load would be insufficient to offer benefit. Some therapeutic vaccine developers have unfortunately been slow to acknowledge this shift in the research landscape; for example, Bionor Pharma conducted a trial attempting to show that their candidate Vacc-4x could delay the need to restart ART after a six-month interruption, but the SMART results had already shown that this type of trial design was risky and outdated. The company has since conducted an analysis (not planned in the original trial design) looking at viral loads among study participants, claiming that vaccination was associated with a difference off therapy of around 1 log (22,300 vs. 61,900 copies). But it is known that a viral load of 22,300 copies likely poses long-term health risks and is not low enough to retard disease progression; furthermore, prior studies strongly suggest that the duration of such an effect is likely to be transient.

Third Time's a Charm?

Although it will present a problem for the commercial development plans of some companies, it is clear that the bar for therapeutic vaccines has been raised. The key question has become, Is it possible for a therapeutic vaccine to generate HIV-specific immune responses capable of completely containing viral replication when ART is interrupted? This may seem like a dauntingly high hurdle given results to date, but it dovetails with emerging research that has recently resurrected therapeutic HIV vaccines for the third time. This research is in pursuit of the ultimate goal: a cure for HIV infection.

Presentations at the 2012 Conference on Retroviruses and Opportunistic Infections (CROI) conspired to highlight this new rationale for therapeutic vaccines. A major focus of cure research is identifying and eliminating the reservoirs of HIV-infected cells that persist in the body despite ART (latently infected cells). For several years, scientists have been evaluating compounds that can awaken dormant HIV, but it has been unclear if this strategy will be sufficient to ensure that infected cells are killed. At CROI, Liang Shan from Robert Siliciano's laboratory at Johns Hopkins presented compelling evidence that simply rousing HIV is not sufficient; CD8 T cells are needed to deliver the coup de grace and kill the infected cells. Shan showed that in most people with chronic HIV infection, HIV-specific CD8 T cells were not functional enough to accomplish the task, but required stimulation with HIV antigens prior to being mixed with infected CD4 T cells—essentially a laboratory dish equivalent of therapeutic vaccination. The study was published in the journal *Immunity* on March 8, 2012 and the authors are unequivocal about the implications, writing: "Our study strongly suggests that boosting CTL [CD8 T cell] responses through vaccination prior to virus reactivation may be essential for eradication of HIV-1 infection."

Therapeutic Vaccines Continued from page 9

There is another complementary reason for studying therapeutic HIV vaccines in the context of cure research. Studies have shown that a portion of the latently infected CD4 T cells that persist in the face of ART are specific for HIV antigens, suggesting that stimulation with a therapeutic vaccine might also reactivate the virus in these cells. A study of therapeutic vaccines in children with HIV has offered some support for this idea, as it uncovered evidence of a transient decline in the numbers of latently infected CD4 T cells during immunizations. An ongoing trial in adults—named Eramune O2—intends to explore this possibility in greater detail.

The Road Ahead

Despite the history of controversy and uncertainty, the ascendancy of cure research has provided a strong and scientifically sound rationale for further studies of therapeutic HIV vaccines. The goals are now far clearer: to achieve containment of HIV replication and prevention of disease in the absence of ongoing treatment (now described as a “functional cure”), or complete elimination of the virus (a “sterilizing cure”). The first evaluations of therapeutic vaccines in this new context are getting underway, but significant questions remain to be answered, particularly in terms of delineating the ideal immune responses that should be induced and evaluating whether they can be effective and sustained. Researchers also need to explore which other antilatenacy strategies should be combined with therapeutic vaccines, and whether different vaccine candidates should themselves be combined to achieve the best results. There might even be a role for therapeutic vaccines in the context of gene-therapy approaches, as a means to boost numbers of gene-modified, HIV-specific CD4 T cells. While there is clearly some road ahead, there is at least a sense, finally, that therapeutic HIV vaccines are headed in the right direction. •

What You Don't Know, You Can Sell

(Continued from page 1)

Despite outrage from activists, Merck refused to study drug-drug interactions (DDIs) between boceprevir (Victrelis), their HCV protease inhibitor, and drugs commonly used to treat HIV, putting coinfecting study volunteers at risk for drug-drug interactions in their own clinical trial.

Drug-drug interactions can have serious consequences for HIV/HCV-coinfecting people, who risk forfeiting current and future treatment options for HIV and possibly HCV as well. DDIs can lower drug concentrations to an ineffective level, leading to drug resistance, or increase drug concentrations, worsening side effects and leading to treatment discontinuation; they can even be life-threatening, as was the case with ribavirin and didanosine (DDI; Videx).

The boceprevir coinfection study opened in mid-2009, before Merck had performed drug-drug interaction studies with HIV protease inhibitors in healthy volunteers, a common step in drug development. Nonetheless, coinfecting study volunteers were allowed to use them; in fact, by default, HIV protease inhibitors—or Merck's own integrase inhibitor, raltegravir (Isentress)—were the only HIV treatment options for study volunteers, since non-nucleoside reverse transcriptase inhibitors were not allowed. Activists kept asking Merck to perform DDIs throughout boceprevir's development, but Merck's attitude remained cavalier; they did not launch key drug-drug interaction studies until two years later, months after boceprevir was approved.

The results of DDI studies with three ritonavir-boosted HIV protease inhibitors, atazanavir/r (Reyataz), darunavir/r (Prezista), and lopinavir/r (Kaletra) in healthy volunteers (rather than the actual trial participants who were using boceprevir with HIV protease drugs for almost a year)

were presented in March at the 19th Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle. The news was not good. Combining boceprevir with these HIV protease inhibitors lowered concentrations of each HIV protease inhibitor, at both the highest and lowest (peak and trough) levels.

Boceprevir lowered the peak concentration of atazanavir/r by 25 percent, and the trough by 49 percent; darunavir/r peak decreased by 36 percent and trough by 59 percent; for lopinavir/r, coadministration with boceprevir dropped the peak concentration by 30 percent and trough by 43 percent. In turn, boceprevir levels dropped by 45 percent when coadministered with lopinavir/r and by 32 percent when administered with darunavir/r; only atazanavir/r had no effect on the concentration of boceprevir.

Failure to characterize these drug-drug interactions put study participants—and coinfecting patients—at an unacceptable level of risk, although clinical implications—or real-life impact on HIV and hepatitis C treatment outcomes—of these drug interactions are not clear. Nonetheless, the U.S. Food and Drug Administration warned that “drug interactions between the hepatitis C virus (HCV) protease inhibitor Victrelis (boceprevir) and certain ritonavir-boosted human immunodeficiency virus (HIV) protease inhibitors (atazanavir, lopinavir, darunavir) can potentially reduce the effectiveness of these medicines when they are used together.”

Regulators from the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) went a step further, recommending that “doctors treating patients co-infected with hepatitis C and HIV should be aware of the findings of the drug interaction study. They should not

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co-administer Victrelis with ritonavir-boosted darunavir or lopinavir in HIV and hepatitis C co-infected patients. Co-administration of Victrelis with ritonavir-boosted atazanavir may be considered on a case-by-case basis if deemed necessary in patients with suppressed HIV viral loads and with an HIV strain without any suspected resistance to the HIV regimen. Increased clinical and laboratory monitoring is warranted.”

Vertex's rival protease inhibitor, telaprevir (Incivek) has outsold boceprevir: in the fourth quarter of 2011, telaprevir trounced boceprevir \$456.8 million to \$87 million. The opportunity to capture the coinfection market share may have motivated Merck's decision to delay drug-drug interaction studies. HCV is more likely to be diagnosed and treated in HIV-positive people than people with HCV alone, for several reasons. HIV treatment guidelines recommend HCV testing for all HIV-positive people; the infrastructure to deliver treatment is already in place; and hepatitis C is known to be more aggressive in people with HIV, so physicians and patients are more game to try for a cure.

After Vertex reported drug interactions between telaprevir and ritonavir boosted HIV protease inhibitors, boceprevir became a more attractive option for co-infected people. Merck's vice president of clinical research, Robin Issacs, alluded to off-label use in the company's February 8 press release. “Though VICTRELIS is not indicated for the treatment of chronic HCV in those who are also infected with HIV, we recognize that some physicians have prescribed or may be considering prescribing VICTRELIS for patients taking ritonavir-boosted HIV protease inhibitors. We felt it was important to share these data as part of our commitment to patient safety and transparency.”

Where was Merck's commitment to safety during boceprevir's development? We can only hope that no patients have been harmed.

The boceprevir experience underscores the importance of timely DDI studies. There are other medications used by people with hepatitis C—whether or not they are coinfecting with HIV—that warrant study, such as methadone, buprenorphine, and commonly prescribed psychiatric medications. Merck representatives have stated that the company will be more proactive with their promising second-generation hepatitis C protease inhibitor, MK-5172.

Activists have released a statement calling on regulatory agencies and pharmaceutical companies to study DDIs between experimental HCV drugs that are broken down by the body in a similar way with hormonal contraceptives, methadone, buprenorphine, lipid lowering agents, immunosuppressive drugs, herbal remedies, and commonly prescribed psychiatric medications in addition to HIV medications. Online at: www.treatmentactiongroup.org/hcv .

New HCV Protease Inhibitor Fact Sheets in English and Spanish

Incivek and Victrelis fact sheets describe how each drug should be used, how likely treatment is to be successful, common side effects, drugs that cannot be used with each HCV protease inhibitor, and information about co-pay assistance and patient assistance programs. Available online at: www.treatmentactiongroup.org/hcv/factsheets

Childhood TB Advocacy Picks Up Steam

by Coco Jervis

The neglected crisis of childhood tuberculosis (TB) is finally garnering some long-overdue attention. TAG hosted Forgotten But Not Gone: Childhood TB, a federal advocacy dialogue and strategy session in Washington, D.C. this January. We brought together over 50 researchers, clinicians, implementers, and global advocates from the TB, HIV, and maternal- and child-health communities to advance the discussion.

While TB remains a leading killer of children worldwide, prevention, diagnosis, and treatment of TB in children have been largely absent from the global public health agenda. It is estimated that of the nine million new cases of TB each year, one million occur in children under the age of 15. However, since many cases go undetected or unreported, the number of children with TB may in fact be vastly higher. Making matters still more urgent, the death of one in three children with AIDS is caused by TB. The reason that childhood TB remains a neglected disease goes beyond just lack of accurate numbers; it is also because of perception. There is a prevailing belief in the public-health community that children with TB are not contagious, and policy makers have been led to believe that treating adults is enough. These beliefs belie the truth that new approaches to preventing and diagnosing TB in infants and children, particularly those with HIV, are desperately needed.

One of the highlights of the January meeting was an incredibly moving personal account of hardship and struggle by a young Texas mother whose toddler son was diagnosed with drug resistant TB meningitis over a year ago. Other speakers provided engaging analysis of the need for more research on a better vaccine; pediatric dosing of new and old drugs; and more effective diagnostics and infection control. One speaker, Jeffrey Starke, a professor of pediatrics at the Baylor College of Medicine who also works at Texas Children's Hospital lamented the fact that children with untreated latent TB often grow up to be adults with active TB. “The opportunity to intervene when they were young was missed,” said Starke, which is why “there's probably more TB now than at any other time in the history of mankind.”

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Childhood TB Advocacy Continued from page 11

January's federal advocacy meeting had two important outcomes. First, everyone agreed that more needs to be done to advance awareness of and action on childhood TB treatment, care, and research; meeting participants joined working groups and are taking concrete steps to deepen their engagement with these issues. Second, the WHO and the Stop TB Partnership have made the goal of zero TB deaths in children the main theme and advocacy call for this year's World TB Day (March 24). TAG has been working with advocates on the international level to develop a roadmap for advocacy, and cohosting congressional TB briefings to highlight childhood TB advocacy. •

Two New Publications for World TB Day

TAG and the Sentinel Project on Pediatric Drug-Resistant Tuberculosis launched a special publication on pediatric drug-resistant TB to build further momentum in the fight against childhood TB. ***Being Brave: Stories of Children with Drug-Resistant Tuberculosis*** documents the challenges children with drug-resistant TB face. Focusing on 15 children in seven countries, some stories show that without prompt diagnosis and treatment, children die from drug-resistant TB. Others demonstrate that, with access to quality medical services, pediatric drug-resistant TB is curable. Yet even in successful cases, diagnosing and treating the disease is lengthy, difficult and painful for children and their families. This collection of stories is a testament to the need to improve both research and access to quality vaccines, diagnostics and drugs to fight TB in children. Read it online at www.treatmentactiongroup.org/tb

Updated Report Shows TB R&D Dramatically Underfunded in 2010

The need for accelerated research to fight TB is clear. Yet new data released by TAG and the Stop TB Partnership showed the global investments in TB research and development (R&D) at just \$630.4 million—less than one-third of the \$2 billion annual target required to eliminate TB by 2050—and the smallest year-to-year increase (2%) since 2005. With fewer than 5% of people with drug-resistant TB receiving treatment, and a point-of-care test for TB only a distant hope, TB R&D funding needs a dramatic ramp-up. *Tuberculosis Research and Development 2011 Report on Tuberculosis Research Funding Trends, 2005–2010, 2nd Edition* is available at www.treatmentactiongroup.org/tb

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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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