On a Darkling Plain—The Years of Despair

Before the Discovery of HAART

And we are here as on a darkling plain
Swept with confused alarms of struggle and flight,
Where ignorant armies clash by night.

—Matthew Arnold, “Dover Beach”

by Mark Harrington

This is the second in a series looking back at the first two decades of TAG’s work to speed up AIDS research. In Part I: TAG’s early campaigns to reform the National Institutes of Health (NIH) AIDS research, boost the federal budget, and revitalize HIV basic science research. Here we look at the clinical science of AIDS before the discovery of highly active antiretroviral therapy (HAART) in 1995–96, and how TAG responded to the needs of people with AIDS.

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

For most of the early 1990s, it seemed that the science of HIV treatment was going backwards. In 1987, AZT became the first Food and Drug Administration (FDA)-approved AIDS drug, giving hope to researchers and people with AIDS alike that this seemingly untreatable virus could be tamed.

Cure-Related Research at AIDS 2012

by Richard Jefferys

At the recent International AIDS Conference in Washington, D.C. (AIDS 2012), the research effort to develop a cure for HIV infection attained a higher profile than it ever has in the past. At a press conference on July 19, the International AIDS Society (IAS) officially launched its Global Strategy “Towards an HIV Cure,” in conjunction with a two-day symposium that immediately preceded the main conference. The IAS strategy is chaired by Françoise Barré-Sinoussi and Steven Deeks and involves a multiplicity of stakeholders, including TAG. Details are available free online in a document titled “Full Recommendations, 1st Edition, July 2012.” A shorter summary and commentary have been published in the journals Nature Reviews Immunology and Nature, respectively. In essence, the strategy is a scientific review of the obstacles to curing HIV (as they are currently perceived) and possible approaches to overcoming them. Among the goals is to enhance collaboration among stakeholders and attract new sources of funding to support cure research.

The Future of TB in the United States: Going, or Growing?

by Erica Lessem

This summer, Treatment Action Group (TAG) and its partners in fighting tuberculosis (TB) issued a call for zero TB deaths, zero new TB infections, and zero suffering from TB [see page 11]. Yet the U.S., long a leader in TB elimination efforts, is in jeopardy of losing ground in the struggle to get to zero. Drug shortages, coupled with financial obstacles, are threatening the success of TB programs nationwide. TB, long forgotten by the general public and by many policy makers, still affects the U.S., with over 10,000 new cases in 2011.

The number of people infected with TB bacteria but not yet sick is even greater, amounting to almost 11 million, according to estimates from the U.S. Centers for Disease Control and Prevention (CDC). There is safe and effective therapy to prevent latent infection from developing into active TB disease. In fact, in 2011 the CDC approved a new therapy that shortened the prevention regimen from nine months of daily isoniazid (a common anti-TB drug) to just twelve once-weekly doses of isoniazid and another anti-TB drug, rifapentine. This dramatic advance could spare patients time and literally hundreds of pills. Currently, an
The NIH auctioned off two AZT-like drugs, ddI and ddC, to drug companies for development. In 1991, ddI (Bristol-Myers Squibb’s didanosine) was approved based on changes in a surrogate marker—a small rise in CD4 T cells in people receiving ddI, versus a continued decline among those on AZT—before the study’s final results demonstrated whether the CD4 cell increase predicted actual clinical benefit.

Early in 1992, the FDA formally issued regulations for accelerated approval to allow marketing of a drug for AIDS and other serious or life-threatening diseases based on such early changes in surrogate markers. It seemed like a great victory for the AIDS activists who had long struggled for such regulatory reform.

In April 1992, Hoffmann-La Roche submitted a new drug application (NDA) for accelerated approval of ddC (zalcitabine). I was an ad hoc community representative for the FDA Antiviral Drugs Advisory Committee hearing. It was not a pleasant task. The data on ddC were difficult to interpret. The drug had serious side effects including potentially crippling nerve pain. But a strong consensus for approval emerged among the AIDS activists at the hearing. I voted to approve ddC—not because it looked effective, but because of the desperate need for new treatments. A closely divided FDA advisory committee recommended a narrow approval.

The benefits of these drugs were short-lived in the case of ddI, and nonexistent with ddC. The difficulties of HIV treatment research in the early 1990s could be summarized as a vicious cycle caused by a combination of bad drugs, badly designed clinical trials, and inadequate measures or markers of anti-HIV drug activity.

**Bad Drugs**

First, the drugs. Virtually all the drugs under study in the early 1990s—ddI, ddC, as well as the subsequently approved d4T (stavudine, 1994) and 3TC (lamivudine, 1995)—were nucleoside reverse transcriptase inhibitors (RTIs). The nucleosides block the HIV protein reverse transcriptase from turning viral RNA into DNA by prematurely terminating the DNA chain, making it impossible for the virus to fully replicate. They differed, however, in their potency (anti-HIV activity), duration of effect, as well as in their toxicity.

AZT attacked the bone marrow, causing anemia. DdI, ddC, and d4T caused serious nerve damage, and sometimes pancreatitis. 3TC appeared the most benign of the first five nucleoside RTIs approved by FDA, but it was also the last to market.

By themselves, none of the nucleosides worked for very long against HIV. According to National Cancer Institute (NCI) virologist John Coffin, these drugs, used singly, caused “little” virus suppression. His measurements were based on viral RNA measurements—so-called viral load tests—which were not yet available in the early 1990s to most researchers, let alone to doctors and patients.

**Badly Designed Clinical Trials**

According to the well-known dogma of combination therapy for difficult-to-treat infections—when studies in the 1950s for tuberculosis made it possible for the first time to cure the disease—it is necessary to use two or more active agents against an organism that rapidly develops resistance to one drug used alone. As early as 1989, when ACT UP’s Peter Staley and I met with chain-smoking Burroughs-Wellcome virologist and AZT supremo David Barry at Research Triangle Park, North Carolina, he told us that the future of HIV treatment lay in combination therapy.

The federally funded researchers at the NIH’s AIDS Clinical Trials Group (ACTG) knew this. But most of them had worked only on herpes, a virus against which a single drug—acyclovir, discovered and brought to market in the early 1980s—worked for most people.

The ACTG’s early attempts at anti-HIV combination therapy would have been laughable had they not resulted in so many failed studies and wasted lives. Approaches such as one week of AZT alternating with one week of ddC were a recipe for the rapid emergence of resistance to both drugs. More often, they added a single new drug to an already-failing monotherapy. The most notorious of these studies, ACTG 155, compared AZT with ddC alone and with a combination of AZT + ddC in a group of people who had already been on—and most likely developed resistance to—AZT.

In spring 1993 came more bad news—the British-French Concorde study showed that early use of AZT (taken before the onset of symptoms and when CD4 T cells were still between 200 and 500 cells/mm3) didn’t provide any benefit over the longer study period.

In response, TAG intensified our work as a watchdog over the ACTG and industry studies of anti-HIV drugs, and deepened our expertise in clinical trial design, statistics, and HIV pathogenesis. We participated in and criticized the studies designed and carried out with public and private funds alike. We were members of key ACTG committees and met frequently with each company making a potential AIDS drug.

In June 1993, TAG and our colleagues witnessed the collapse of all the early hopes for combination therapy at the International AIDS Conference. As David Barr wrote for TAGline in 2003:

“In Berlin, two central ideas at the heart of the treatment strategy were disproved. The first was that early use of AZT was beneficial. This was not a surprise, as the results from the Concorde study only proved what most people with AIDS on AZT found out the hard way: the drug stops working when used alone... The results of ACTG 155... showed that the two drugs did no better than one in helping people failing on AZT mono-
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therapy. The bug was still mightier than the drug.

This was depressing enough. What made it even more depressing—and infuriating—was that NIAID [the National Institute of Allergy and Infectious Diseases] and the researchers involved in the study skewed their reports on the study results. Instead of presenting the results of the planned analysis, which showed the AZT+ddC combo as ineffective, an unplanned and statistically underpowered substudy analysis was performed which showed, in one of the arbitrary T-cell groupings, that patients on two drugs did “better” than the other patients.... Margaret Fischl...started presenting the post hoc substudy analysis, and we all lost it.

Mark Harrington, Gregg Gonsalves, Derek Link and I were all there, and we got up and just started to scream that this was a pack of lies. Dr. Fischl got all flustered. I got up from my seat and went to the microphone and started yelling that she was not telling the truth. She responded and had to admit that the planned results of the study were the exact opposite of what she was presenting. We continued to yell. The audience knew we were right and started applauding our comments. Finally, we all walked out of the auditorium.”

As I wrote at the time in The Crisis in Clinical AIDS Research:

“After the Berlin conference,... [chief ACTG statistician] Steve Lagakos commented to one community member that “those activists wouldn’t be so mad [about the much-hyped “subset trend analysis” from ACTG 155] if the drugs were better.” Well that’s right Steve—if the drugs were better, then the trials wouldn’t need to be bigger, or better designed, or analyzed more honestly—in fact, if the drugs were good enough, we might not need answers from randomized trials at all, as in the case of ganciclovir [DHPG]. But the drugs aren’t better—and that’s why we turn to statisticians in the hope that they will help design studies competently, and analyze them honestly, keeping in mind that the primary goal is the development of information useful to patients and their providers.”

Indeed, in ACTG 155 it appeared that combination therapy was 50% more toxic than either monotherapy, but no more effective.

So by mid-1993 it was apparent that our hopes that early and limited CD4 cell increases would reliably predict clinical benefit were unfounded—since ddC had not shown the same benefits earlier seen with ddl—and that two drugs, at least in experienced patients, were no better, and possibly worse, than one drug.

No results were available yet on whether two drugs started at the same time—among people who had never taken anti-HIV drugs at all (combination theory postulated that two might delay resistance from emerging as quickly as it did with a only one drug)—were better than one. ACTG 175 was one such study, comparing AZT alone to ddl alone to AZT + ddl. Its results wouldn’t come in until late 1995.

In the meantime, d4T crawled forward as the next anti-HIV drug submitted for FDA approval, in mid-1994. The Alice-in-Wonderland quality of HIV drug development at that time was well captured in a New York Times story headlined, “F.D.A. Panel Recommends AIDS Drug Despite Incomplete Data”:

“A panel of scientists recommended today that the Government approve a new drug to battle the virus that causes AIDS, but with strong warnings that doctors still do not know enough about the medicine to say who should take it.

An advisory committee to the Food and Drug Administration said the drug, d4T, or Stavudine, probably provided some benefit over the three existing AIDS drugs. But the panel could not say just who would benefit, just how safe it was or whether the manufacturer was on the right track to answer the many questions.”

TAG and its allies sent a delegation that was frankly split about the drug’s effectiveness, but in agreement that the data as submitted were impossible to interpret. TAG’s Gregg Gonsalves, who was the community representative on the FDA panel at that time, correctly predicted that the pivotal studies by d4T’s sponsor, Bristol-Myers Squibb, would be too small to prove that the drug worked. TAG’s Spencer Cox testified from the public, as did GMHC’s Derek Link. Neither could interpret the data clearly and both pointed out the flaws in the existing paradigm.

The next drug to engage the attention of the community was the first in a new class, the protease inhibitors. This drug was saquinavir. Unfortunately, the sponsor was Roche. At that time, I was a member of the ACTG’s primary infection (HIV treatment) committee. The negotiations between Roche and the ACTG were nontransparent, to say the least.

Roche had failed to find a maximum-tolerated dose of saquinavir, so we did not know whether the dose they were moving into phase II was the best possible dose in humans. The company refused to provide the committee with its preclinical or phase I data. Instead, it took the two principal investigators (PIs) into the hallway, showed them the data, and the PIs came back and told the rest of the committee that the saquinavir dosing data looked fine. They proceeded to enroll a couple hundred patients into another badly designed study, this time comparing two- and three-drug combinations in people who were already failing AZT. ACTG 229 enrolled 302 people and randomly assigned them to AZT/ddC/saquinavir versus AZT/saquinavir versus AZT/ddC (the combination that bombed in Berlin).

Later it became clear that the dose of saquinavir was far too low. Ninety-six percent of the drug was excreted unchanged in the urine, meaning that just four percent of it got into the blood and the body’s cells to block HIV replication. Even at an insufficient dose, however, sa-
quininariv could produce enough anti-
missing activity to lead HIV to become
resistant, not only to saquinavir
itself, but to all the first-generation
protease inhibitors.

Despite the inadequate dose, small study, short duration, and
shoddy data, Roche, undeterred, went to the FDA in midsummer 1994
to request that it consider saquinavir
for accelerated approval.

When Bristol-Myers sought ac-
celerated approval for ddI in 1991,
there had already been over 35,000
people on the drug through expand-
ed access since 1989, and thousands
of people had been in ddI studies
over a five-year period. By contrast,
in mid-1994, saquinavir had been
studied in fewer than a thousand
people for less than a year. Neither
the safety data nor the efficacy—
such as they were—of saquinavir
looked as good as those for ddI
alone had three years earlier.

This time, TAG drew the line. We
were determined that the failures
to study and regulate the approval
of the nucleoside analogues not be
repeated with the protease inhibi-
tors, which looked like a much more
promising class of drugs, even if
saquinavir itself appeared to be rela-
tively weak.

We wrote a letter to and ob-
tained a meeting with FDA Com-
missioner David Kessler—an im-
passioned reformer who was the
intellectual father of accelerated
approval—and the agency’s HIV
drug-review staff.

It wasn’t a friendly meeting. TAG
and our allies criticized the FDA for
failing to hold Roche accountable
for not fulfilling its promised post-
marketing studies for ddC, and for
allowing Roche and other sponsors
to conduct studies that were both
too small and too short to show
whether the drugs worked in the
majority of people with HIV.

TAG presented a plan to ad-
dress these issues for the protease
inhibitors as a class by combining
the best of expanded access with
a better clinical trial design that
was both large and long enough to
show whether adding a protease
inhibitor—or starting with one—was
better than adding or starting with a
nucleoside. Modeled after a series
of successful cancer and heart disease
studies, we called this a large, simple
trial (LST).

TAG had rushed into the FDA
meeting and the LST proposal
without sharing our ideas quickly or
broadly enough with the wider com-

unity. The death rate from AIDS
was still climbing and in our haste
to change the direction of the ship
we neglected to inform or collabo-
rate with our fellow comrades in the
crew.

This haste backfired on us later
that summer when *Barron’s* business
magazine published a provocative
interview with TAG’s Spencer Cox
criticizing the saquinavir trials with
the even more provocative headline,
“Do We Have Too Many Drugs for
AIDS?”

Quickly, TAG became the most
unpopular organization in the AIDS
activist world. During the late sum-
mer and early fall, we retreated,
putting forward our position in a re-
port, *Rescuing Accelerated Approv-
al: Moving Beyond the Status Quo*,
which we distributed at a heated
FDA advisory committee hearing in
September 1994, where the debate
reached impassioned levels.

As HIV gastroenterologist Donald
Kotler stated in a dramatic scene
from that era, documented in David
France’s *How to Survive a Plague*
(www.howtosurviveaplague.com),
ACT UP was talking about access.
TAG was talking about answers. We
were talking past each other—but all
of us needed both.

Luckily we found allies as well as
detractors. One of the most notable
new allies was the brilliant HIV-
positive activist and virtually self-
taught statistician Carlton Hogan, a
New Yorker in exile in Minneapolis,
Minnesota, where he worked in the
statistical center for the NIH-funded
Community Programs for Clini-
cal Research on AIDS (CPCRA), a
community-inspired and grassroots
rival to the more academically slick
and sometimes self-satisfied ACTG.

**Inadequate Surrogate Markers**

There was no immediate resolu-
tion to the crisis, because there still
weren’t the scientific tools to bet-
ter measure the anti-HIV activity of
different drugs, combinations, and
strategies. CD4 T-cell levels, while
showing some correlation with anti-
 viral activity, were an indirect marker,
and different drugs in the same class
appeared to have consistent effects
on CD4 counts while clinical results
diverged.

Early methods to measure HIV
activity directly yielded conflicting
results. One of the easier methods
was to measure blood levels of the
p24 protein, a component of HIV
that was sometimes measurable at
high levels. In many people, however,
p24 was hard to measure, probably
because it was bound to p24 anti-
odies, gumming up the test.

An even more demanding tech-
nique was quantitative co-culture—
taking blood from the cells of a
person in a study and measuring
how fast that blood could infect
cells in culture. This was difficult,
varied from lab to lab, and could not
be commercially standardized.

But in the earlier phases of re-
search there was, suddenly, promise.

The polymerase chain reaction
(PCR) method of measuring DNA or
RNA sequences by multiplying their
binding to a target genetic sequence
was discovered by Kary Mullis and
colleagues in 1983. By 1989, early
forms of PCR were being applied to
HIV research. In January 1995, David
Ho and colleagues from New York’s
Aaron Diamond AIDS Research
Center (ADARC) showed in a study
of quantitative PCR that unlike the
nucleosides, more potent protease
inhibitors such as Abbott’s ritonavir
could reduce HIV levels by 99% (two
logs of 10) within two weeks. (The
weakest nucleoside, ddC, reduced
HIV by only one-half log.) However,
when protease inhibitors were used
alone, drug resistance soon emerged
as well.

Now researchers had a tool to
measure—and to try to prevent—
the rebound in viral replication that
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occurred so quickly after an initial decline on any single drug.

In February 1995, at a hearing of the National Task Force on AIDS Drug Development, TAG and GMHC delivered a series of recommendations to the manufacturers for each protease inhibitor. We recommended that Roche double the size of its pivotal saquinavir efficacy trials. We were scathing about Merck’s studies of L-735-524 (MK639, later indinavir), calling them “poorly controlled, inadequately powered studies. It appeared that Roche double the size of its pivotal saquinavir efficacy trials. We were scathing about Merck’s studies of L-735-524 (MK639, later indinavir), calling them “poorly controlled, inadequately powered, and unlikely to provide useful information on the drug’s clinical utility.”

However, the activists praised Abbott for adopting a “novel ‘standard-of-care’ control arm [in its studies of ABT-538 (ritonavir)]....[allowing patients to take any nucleoside analogue they wish, with the possible exception of 3TC...[and] then be randomized to receive either ABT-538 or a matching placebo.” This control arm had originally been proposed by Spencer Cox of TAG.

Later in 1995, the first study demonstrating clear clinical benefit to combination therapy was announced. It was a by-now-retrograde comparison of AZT alone, ddI alone, AZT + ddI and AZT + ddC. For once, the researchers studied the regimens in people who were not yet already AZT-resistant. The results of the study, ACTG 175, showed that the combination of AZT and ddI was clearly better than AZT alone. However, ddI alone also appeared to be better than AZT alone, and the study wasn’t big enough to conclusively show that two drugs were better than one.

Another study with early results showed something even more promising. Abbott presented some tantalizing early results of ritonavir as monotherapy and in combination. As TAG reported at the time in TAG does ICAAC:

“D. Norbeck...described a French triple-combination study...Participants were given AZT/ddC/Ritonavir. Their CD4s went up by 110 and their plasma RNA went down by 2.5 logs at 20 weeks. Over the subsequent weeks, he claimed, an increasing proportion of participants became viral culture negative—which is to say, they could not culture infected cells from the blood. “Some became PCR and culture negative, which suggests that the viral reservoir was empty.”

We were so used to unsubstantiated or later-to-be-discredited industry—and, for that matter, academic and NIH—hype that we were instinctively incredulous at Abbott’s claim for the unprecedented ability of a triple combination including two mediocre drugs—AZT and ddC—plus the superpotent but also new and untried ritonavir, to render viral cultures negative or viral load in the blood undetectable.

The year ended with a whimper, not a bang. The FDA gave stavudine (d4T) full approval, despite the inadequately powered studies. It approved Glaxo Wellcome’s new mover drug 3TC. And it gave accelerated approval to Roche’s saquinavir, the first protease inhibitor approved, and also the weakest.

In the United States, the wave of AIDS-related illness and death crested in 1995. By 1995, just fourteen years after the disease was identified, the New York Times reported that AIDS had become the leading cause of death among Americans ages 25–44. In that year, cumulative U.S. AIDS deaths (311,381) as reported by the CDC surpassed the total U.S. battlefield deaths in World War II (291,557).

More Americans died of AIDS in 1995 alone (50,798) than on the battlefields of Vietnam during the entire course of that war (47,434).

It didn’t seem like drug development was making a dent in the relentless piling up of bodies.

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Only Stronger U.S. Leadership Can End the AIDS Epidemic

Existing treatment and prevention techniques could prevent millions of new HIV infections and deaths from AIDS—but only if Obama sustains funding.

by Mark Harrington

This article was first published on 24 July 2012 in theAtlantic.com.

Four years ago, President Obama’s election generated hope for new American leadership in the fight against AIDS here at home and around the world. On that day, South Africa’s Treatment Action Campaign — the movement which combined massive demonstrations with sophisticated insider legal cases and science-based activism to force South Africa to create the world’s largest HIV treatment program — recalled his visit to their offices in the township of Khayelitsha, Western Cape, in August of 2006, and how it had urged him to run for president to have a chance to fulfill his commitment to addressing AIDS. “Obama took a strong position on preventing and treating HIV/AIDS,” the group recalled in 2008, “and was critical of President Mbeki and the South African government’s response to the epidemic,” then expressed through a deadly form of HIV denialism.

Since becoming president, Obama has continued to talk the talk, promising last December on World AIDS Day to lead the way towards an AIDS-free generation, and to increase U.S. support for global HIV treatment to cover antiretroviral therapy (ART) for six million people around the world by the end of 2013. That makes his silence this week, during the first International AIDS
Conference to be held on American soil since the 1990 gathering during the George H.W. Bush administration, all the more striking.

Obama simply hasn’t walked the walk when it comes to funding for AIDS. In fact, earlier this year, he proposed a shocking cut of $550 million to the President’s Emergency Plan for AIDS Relief (PEPFAR), the most successful U.S.-funded global health program in history.

At first, the administration failed to provide any explanation for such drastic cuts, which could put the lives of thousands who depend on the United States to pay for treatment at risk. Later, in response to pressure from the Treatment Action Group and its activist colleagues, administration officials claimed that they had been so successful in reducing costs that they could reach the target of getting medicines to 6 million during 2013 even with dramatically reduced funding.

It’s true that costs have gone down. Earlier this week, the Clinton Health Access Initiative released data showing that the cost of providing HIV care and treatment has dramatically fallen in the past two years due to increased use of generic medications and overall program efficiencies. The annual cost of HIV care in Ethiopia, Malawi, Rwanda, and Zambia — including drugs, lab costs, and health worker salaries — is now just $200, while in more developed South Africa it is $682. In her speech to the International AIDS Conference on Monday, Secretary of State Hillary Clinton indicated that these economies of scale enabled PEPFAR-supported programs to enroll 600,000 people in the last six months, compared with 700,000 in the past fiscal year.

With these successes in hand, the Obama administration could easily have proposed a more rapid scale-up towards unmet HIV prevention and treatment needs, rather than slashing PEPFAR. There are plenty of global health needs to which the funds saved on “efficiencies” could have been applied — expanding TB testing in mothers and children, purchasing GeneXpert TB test kits, which can diagnose the disease and its most common drug-resistance patterns in two hours rather than the two weeks or more traditional TB culture takes — as well as expanding ART treatment slots and growing maternal and child health programs. All these would have been steps forward towards the making administration’s AIDS-free generation promise a reality.

Instead, the administration decided to pocket the savings, leaving millions of people out in the cold. Some people even wonder if the president’s lack of enthusiasm for PEPFAR heralds the program’s demise next year, when it is due to be reauthorized by Congress. PEPFAR was launched in 2003 by President George W. Bush and, along with the Global Fund to Fight AIDS, Tuberculosis and Malaria, has channeled $39 billion in U.S. aid towards HIV treatment and prevention efforts (as well as the fights against TB and malaria) around the world, making the United States the single largest source of dollars addressing the global HIV pandemic. Four-and-a-half million people today are receiving life-saving HIV treatment through PEPFAR in low and middle-income countries in Africa, Asia, the Caribbean, and South America.

Had Obama attended the International AIDS Conference (Secretary of State Hillary Clinton, HHS Secretary Kathleen Sebelius, PEPFAR chief Eric Goosby, and NIH AIDS supremo Anthony Fauci and other members of the administration have been speaking or attending in his stead), he would have heard deep gratitude for the U.S. role in responding to the HIV epidemic around the globe. He would have heard optimism that the world is on the cusp of being able to do something long thought unthinkable — actually bring about an end to the AIDS pandemic.

But since he won’t be there, here’s a to do list the president should consider if he wants to walk the walk to truly begin to make that happen:

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1. Fully fund PEPFAR and support its reauthorization in 2013. Restore the $546 million in proposed cuts to PEPFAR in fiscal year 2013, and begin planning now for the program’s upcoming legislative reauthorization in 2013.

2. Restore cuts to the Centers for Disease Control and Prevention (CDC) tuberculosis program. TB is the leading cause of HIV related death worldwide, yet the last budget continues a deplorable pattern of cutting the CDC’s TB control budget. As a result of the cuts, the New York City Department of Health is being forced this week to suspend an innovative pilot program to treat cases of latent TB infection with a three-month course of treatment, instead of the older standard nine-month course, which imposes much greater inconveniences on patients and health workers alike.

3. Fully support the Global Fund to Fight AIDS, Tuberculosis and Malaria, and enable it to replenish depleted funding coffers for countries trying to expand their programs for prevention, care, and treatment of the three diseases, which often spread in tandem and occur at the highest rates in the same countries.

4. Reject the congressional ban on federal funding for needle exchange. As part of last year’s budget deal, Obama conceded to congressional demands that the ban on federal funding for needle exchange be reinstated. The administration did this despite knowing that needle exchange programs save lives and reduce HIV transmission — and despite having reversed the previous ban. Last year’s decision was wrong and could lead to unnecessary increases in HIV incidence among drug users and their sex partners.

5. Revise and revitalize the National HIV/AIDS Strategy (NHAS) to incorporate new scientific findings and to more rapidly scale up HIV prevention and treatment programs nationally. A recent paper by David Holtgrave, a department chair at the Johns Hopkins Bloomberg School of Public Health, and colleagues found that “[w]ithout expansion of diagnostic services and of prevention
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services for [people living with HIV], scaling up coverage of HIV care and treatment alone in the U.S. will not achieve the incidence and transmission rate reduction goals of the NHAS. However, timely expansion of testing and prevention services for [people living with HIV] does allow for the goals to still be achieved by 2015, and does so in a highly cost-effective manner.” The goals of the NHAS include:

- lowering new HIV infections by 25 percent and HIV incidence by 30 percent
- increasing Americans’ knowledge of their own serostatus from 79 percent to 90 percent
- increasing the proportion of newly diagnosed Americans linked to clinical care within three months from 79 percent to 90 percent
- increasing the proportion of Ryan White HIV/AIDS program clients who are in continuous care (at least two visits for routine HIV medical care in 12 months at least 3 months apart) from 73 percent to 80 percent
- increasing the percentage of Ryan White HIV/AIDS program clients with permanent housing from 82 percent to 86 percent, and
- increasing the proportion of HIV-diagnosed gay and bisexual men, Blacks, and Latinos/Latinas with an undetectable viral load by 20 percent each

all by the end of 2015.

Recent scientific discoveries have shown that earlier initiation of antiretroviral therapy can reduce HIV transmission by a whopping 96 percent among couples with differing HIV status. This led Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) to write:

“The fact that treatment of HIV-infected adults is also prevention gives us the wherewithal, even in the absence of an effective vaccine, to begin to control and ultimately end the AIDS pandemic....For the first time in the history of HIV/AIDS, controlling and ending the pandemic are feasible; however, a truly global commitment...is essential. Major investments in implementation now will save even greater expenditures in the future; and in the meantime, countless lives can be saved.”

Revising the National AIDS Strategy to incorporate these new findings could enable the administration to set more ambitious targets of reducing HIV transmission and incidence by 50 percent or more — as South Africa has committed to doing by 2016 — increasing linkage to care to 95 percent, increasing Ryan White care retention to 95 percent (the program funds care for those who cannot otherwise afford it), increasing Ryan White clients’ access to housing to 95 percent, and increasing the proportion of Blacks, Latinos and Latinas, and gay men with an undetectable viral load to at least 90 percent.

Of course, this revised National AIDS Strategy would cost more money up front. But as Fauci pointed out above, and as Bernhard Schwartländer of UNAIDS, who first proposed the scale-up efforts that led to PEPFAR and the Global Fund in a pivotal paper in Science magazine in 2001, and colleagues pointed out in their global strategic investment framework for HIV:

“[t]he yearly cost of achievement of universal access to HIV prevention, treatment, care, and support by 2015 is estimated at no less than US $22 billion. Implementation of the new investment framework would avert 12.2 million new HIV infections and 7.4 million deaths from AIDS between 2011 and 2020 compared with continuation of present approaches, and result in 29.4 million life-years gained. The framework is cost effective at $1060 per life-year gained, and the additional investment proposed would be largely offset from savings in treatment costs alone.”

6. Increase funding for the National Institutes of Health (NIH) by 15 percent annually for the next five years. The NIH budget has been flatlined since 2004, with the exception of two years of stimulus funding in 2010-2011. The rate at which new grant applications are funded has fallen to 10 percent, meaning nine out of 10 applications are rejected. In his 2011 State of the Union address, Obama committed to reinvigorating the United States’ commitment to and investment in scientific research:

“This is our generation’s Sputnik moment. Two years ago, I said that we needed to reach a level of research and development we haven’t seen since the height of the Space Race. And in a few weeks, I will be sending a budget to Congress that helps us meet that goal. We’ll invest in biomedical research, information technology, and especially clean energy technology — an investment that will strengthen our security, protect our planet, and create countless new jobs for our people.”

This year, his proposed 2013 budget flatlines NIH once again. We need increased investment in biomedical research to assure the discovery and development of the innovative tools we need to end the epidemic, cure HIV and find a vaccine to prevent its transmission.

7. Commit the administration to fully funding the research, prevention, care, and treatment scale-up required to end the pandemic. Some of the steps needed to end AIDS are discussed in a report issued this week by our colleagues at AVAC and amfAR, An Action Agenda to End AIDS.

President Obama has shown himself capable of the vision to create a National HIV/AIDS Strategy and continued to ensure that the United States is the leader in support for global HIV programs. Now is the time for him to embrace the newest scientific results, which give America the power to map out an endgame for the epidemic around the world.
Presentations and video from the IAS symposium, held on July 20 and 21, will be available online soon. Because abstracts were selected from submissions to AIDS 2012, many of the studies discussed at the symposium—including those by Fabio Romerio and Timothy Henrich, described below—were subsequently presented at the conference and can already be viewed on the website. A summary of the meeting will be published in a forthcoming issue of the *Journal of the International AIDS Society*.

The VISCONTI Cohort

Among the most publicized data presented at the IAS symposium related to a French cohort (dubbed the VISCONTI cohort) comprising 14 individuals treated within ten weeks of infection who, after an average of around three years on antiretroviral therapy (ART), interrupted treatment and have subsequently maintained control of viral load to less than 50 copies/mL for an extended period (a median of 6.6 years; range: 4–9.5 years). This study was the focus of an overview talk by Asier Sáez-Cirión and an abstract presentation by his colleague Christine Bacchus. Preliminary results have been published and presented before: in a letter to the journal AIDS in 2010, five cohort members controlling viral load off ART for a median of 6.25 years—designated post-treatment controllers (PTCs)—were described (out of a total of 32). At the Conference on Retroviruses and Opportunistic Infections (CROI) in 2011, a poster presentation reported that the number of PTCs had increased to ten (median duration of control: six years).

Sáez-Cirión updated these results with the information that a total of 14 PTCs have now been identified. Notably, four of these individuals are showing declines in HIV reservoirs (as measured by HIV DNA levels) over time. Sáez-Cirión highlighted a number of unusual features of this cohort that set them apart from elite controllers (individuals who control viral load to undetectable levels in the absence of any treatment). Most importantly, they lack the favorable immune response (HLA) genes that are consistently associated with elite control: HLA B*57 and B*27. Instead, around half the PTCs possess the HLA B*35 allele, which in untreated HIV infection is associated with a significantly increased risk of rapid disease progression. In addition, HIV-specific CD8 T-cell responses are of lower magnitude than those typically seen in elite controllers, and levels of immune activation and HIV DNA are also low.

Sáez-Cirión attempted to assess how frequently the PTC phenomenon occurs after primary infection treatment. In a preliminary look at the French Hospital Database on HIV, 756 individuals were identified who started ART within six months of infection and continued for at least a year. A subset of 74 eventually interrupted ART and of these, 15.7% maintained undetectable viral load for a minimum of two years. Sáez-Cirión also cited a study by Cécile Goujard and colleagues (published shortly after the meeting in the journal *Antiviral Therapy*); in this case, out of 164 participants, 8.5% maintained viral loads below detection for two years after interruption, and 7.2% at three years. In contrast, Sáez-Cirión noted that an analysis of 34,317 HIV-positive individuals in France identified only 81 elite controllers, putting the estimated proportion of individuals likely to attain control of viral load in the absence of any ART at around 0.24%.

The duration of viral load control in the VISCONTI cohort PTCs makes them unusual, and they are receiving attention as a possible model of a “functional cure” in which HIV is suppressed (rather than eradicated) without treatment. But there are many unanswered questions and apparent contradictions with other studies that need to be addressed and resolved. Sáez-Cirión noted that all but one of the 14 individuals had symptomatic primary infection, high viral loads, and low CD4 counts at the time of initiating ART—as he put it, their primary infection appeared “tougher” than is typical. Yet in the Goujard study he cited, the factors associated with becoming a PTC were just the opposite: high CD4 counts and low viral loads (in addition to female sex). An independent analysis of the frequency of PTCs—which the authors acknowledge was prompted by the VISCONTI data—was published in the *Archives of Internal Medicine* on July 23. A total of 259 individuals from the multicountry CASCADE cohort were identified who received ART within three months of infection. The probability of maintaining PTC status 24 months after ART interruption in this analysis was 5.5%, and the characteristics of these 11 individuals did not differ from those of the overall study population. Sáez-Cirión was questioned at the symposium regarding levels of inflammatory biomarkers and any clinical events in the VISCONTI cohort PTCs; he responded that these analyses are ongoing and incomplete. In terms of CD4 counts, Sáez-Cirión stated that only one of the 14 is showing a decline over time. The reason for the apparent overrepresentation of HLA B*35 is as yet unclear; when quizzed on the issue, Saéz-Cirión suggested that possession of this allele may have explained the high prevalence of symptoms in the cohort which, in turn, prompted them to start ART early. However, previously published studies have not reported an association between HLA B*35 and primary infection symptoms. Further complicating the question is the existence of HLA B*35 subsets named Px and Py, and only people possessing HLA B*35 Px have been reported to experience rapid HIV disease progression: the distribution of Px versus Py in the VISCONTI cohort PTCs is as yet unknown.
Cure Research Continued from page 8

Replication-Competent HIV Reservoirs May Be Underestimated

Latency expert Robert Siliciano presented data suggesting that the amount of replication-competent HIV DNA in people on ART may be greater than has been thought. The most commonly cited estimate posits that only around one out of every 100 latently infected resting CD4 T cells harbors replication-competent virus (the reason for the difference being that the majority of the viral DNA is mutated in ways that render it nonfunctional). Siliciano looked at 179 samples of CD4 T cells containing latent HIV that could not be induced to replicate by the standard method of PHA stimulation (PHA or phytohemagglutinin is a substance that triggers CD4 T cell division and thereby activates latent HIV). He found that while the majority of the HIV DNA proviruses were indeed defective (due to lethal hypermutation, deletions, and other alterations), an average of 16.8% (range: 6–36%) were fully intact. Siliciano’s laboratory has cloned these intact sequences and confirmed that the viruses are able to replicate. The results imply that the size of the replication-competent HIV reservoir in people on ART may be 50-fold larger than in prior estimates. However, among the questions that remain to be answered are whether these viruses can be induced to replicate in vivo, and if approaches other than PHA stimulation might be able to coax them out of hiding.

High CD2 Expression as a Marker for Latently Infected CD4 T Cells

The laboratory of Fabio Romero at the Institute for Human Virology in Baltimore has developed an in vitro model of latent HIV infection that attempts to closely mimic the in vivo situation using primary CD4 T cells (as opposed to immortalized cell lines, which may not accurately reflect the biology of cells in the body). In a presentation at the symposium, Romero described the use of this model to identify cell surface markers that may be preferentially expressed by latently infected cells. This is an important goal for cure research, because it could facilitate the targeting of anti-latency approaches to the cells most likely to be infected. The lead candidate that emerged from Romero’s work is CD2, which was expressed at higher levels on infected versus uninfected CD4 T cells. Romero is collaborating with Nicolas Chomont from the Vaccine & Gene Therapy Institute of Florida to investigate whether these results are also reflected in vivo: a preliminary study involving six individuals on long-term ART found that, in all cases, HIV DNA was more commonly present in CD4 T cells expressing high levels of CD2.

Absence of a Detectable HIV Reservoir after Allogeneic Stem Cell Transplantation

Timothy Henrich from Brigham and Women’s Hospital and Harvard Medical School presented two case reports relating to individuals with HIV who received allogeneic stem cell transplants for the treatment of cancer. Strikingly, replication-competent virus can no longer be detected in either individual after around 2 and 3.5 years of follow-up, respectively, and their anti-HIV antibody levels are declining. However, both remain on ART, so it is not known if they are cured (the extensive media coverage Henrich’s talk received was not always clear on this point). Unlike Timothy Brown, the “Berlin Patient,” who received a stem cell transplant from a donor homozygous for the CCR5delta32 mutation, the transplants in both these cases came from individuals with normal CCR5 expression. Further study may thus help reveal whether the CCR5delta32 mutation was necessary for achieving a cure in Brown, or if the transplant itself and associated factors—such as graft-versus-host disease, where the new immune system that develops from the transplant attacks the older host cells—can be sufficient. Plans are under way to conduct analytical ART interruptions to assess if a cure has been achieved in these individuals.

TB in the U.S. Continued from page 1

estimated 300,000 to 400,000 people have begun treatment for latent TB in the U.S., but many do not complete it—remaining at risk of developing active TB. Many more may be eligible to begin treatment, but do not know they are infected, or are unwilling to take nine months of medication for an asymptomatic infection. The simplified 12-dose regimen may encourage more people with latent TB infection to initiate and complete therapy.

Although the shorter-course regimen offers many advantages, health departments face a huge barrier to implementation: the cost of rifapentine. Even the New York City Department of Health and Mental Hygiene, which houses one of the U.S.’s premiere TB programs, can’t afford to implement rollout of the new preventive treatment. Rifapentine, produced by Sanofi-Aventis under the name Priftin, is available to public TB centers under recently reduced federal discounted pricing; however, the per-patient cost of rifapentine is still $115.88, over ten times more than that of isoniazid. Though rifapentine received approval in 1998 and is no longer under patent, there are no generics available. In New York City, where order 3,500 patients with latent TB infection per year are eligible to receive the new regimen in its public clinics, the drug costs alone would be over $443,380, instead of just over $100,000 in total costs for the nine months of isoniazid alone. As the City, like others around the country, faces federal and local budget cuts (described in further detail below), it cannot spend hundreds of thousands of dollars more per year to implement the new therapy, despite a belief that it would improve treatment-initiation and -completion rates.

Drug pricing also endangers the treatment of active TB disease, especially drug-resistant cases. TB programs in the U.S. identified cost as a leading challenge to obtaining medications for multidrug-resistant TB. The average total cost to treat just one person with multidrug-resistant TB in the U.S. is between $500,000 and $1.8 million. The price...
of capreomycin, a crucial injectable agent used for at least six months in the treatment of multidrug-resistant TB, just doubled because of a change in manufacturers.

In addition to rising costs, drug supply issues are imperiling TB programs. The U.S. experienced a record number of drug shortages in 2010—a threefold increase over 2005 shortages. The limited availability of antibiotics and injectables, cornerstones of the treatment for drug-resistant TB, is particularly problematic. Recently, only two of four anti-TB injectables used to treat drug-resistant TB have been available, and only so on an emergency basis.

The causes of these drug stockouts are varied. Often, there is a sole-source provider for second-line drugs, making procurement difficult and unstable. There are shortages of the active pharmaceuticals themselves (this has also been a problem for the first-line drug isoniazid: the main manufacturing plant in the world for the active ingredient in isoniazid was destroyed in the 2011 earthquake and tsunami in Japan). There are delays in manufacturing and shipping, and because many drugs or materials expire quickly, inventory is not kept stocked. Injectables in particular have been found to be contaminated due to unsuitable manufacturing conditions. At times, manufacturers also decide to discontinue products, perceiving the market size or anticipated profits to be small. Finally, some drugs are available only on an investigational-use basis, requiring a long, complex application process to permit their use for TB patients.

These medication shortages are dangerous. They can result in treatment delay, endangering critically ill patients and allowing people with TB to be infectious longer and have more opportunity to transmit the disease. Shortages can also lead to the use of inappropriate treatment regimens or to treatment lapse or interruption, putting patients at risk of side effects or of developing resistance to even more drugs. These shortages also place a huge burden on TB program staff, who have to dedicate excess time to drug procurement.

Given the dual threats of rising costs and shortages of TB drugs, there could not be a worse time for cuts to TB program budgets. Yet city and state TB programs are facing funding shortfalls from the local, state, and federal levels. New York City’s TB program, for example, will have its federal funding slashed by $2 million in 2013, on top of a $300,000 rescission from 2012 and a 10-12% cut in City funding for the next year. A grim warning of the potential results of these and similarly shortsighted budget cuts can be found in the devastating outbreak of multidrug-resistant TB in New York City in the 1990s, which was estimated to have cost at least $1 billion to control. Similarly, over 52,000 excess cases are estimated to have occurred nationwide between 1985-1992, due in part to limited funding for TB in the preceding years.

The U.S. has made enormous progress in the fight against TB, both within and outside of its borders. Yet the country is in jeopardy of falling prey to what the CDC has titled “the low incidence paradox”—the perception that public support to fight TB is no longer necessary, which weakens programs and ultimately leads to an increase in TB. To protect its people and continue to set a global example, the U.S. has a responsibility to maintain and increase its investment in TB programming, and to avoid drug shortages. The CDC and the U.S. Food and Drug Administration (FDA) are making strides toward working with global institutions (such as the Global Drug Facility) to stabilize procurement, and toward helping programs more easily obtain potentially lifesaving second-line drugs.

We can reach zero TB deaths, zero new TB infections, and zero suffering from TB in the U.S., but only if we change the status quo. We are in danger of a reversal in our progress, and we need firm commitments from legislators to maintain (or better yet, increase) funding for TB. Additionally, private-sector commitment, including that of Sanofi-Aventis, to affordable pricing and stable supply of TB drugs is necessary. With political will and private-sector cooperation, our “zero” aspirations can be realized.

What is the current strategy for TB, and why is it inadequate?

The WHO’s Stop TB Strategy has been at the forefront of global TB control since its development in 2006. The Stop TB Strategy anchors its targets to those of the Millennium Development Goals, which include to “halt and begin to reverse the incidence of TB by 2015.” The Strategy therefore aims: 1) by 2015, to reduce prevalence and deaths due to TB by 50% from 1990 levels (reduce prevalence to 155 per 100,000 population, and deaths to 14 per 100,000 per year); and, 2) by 2050, to eliminate TB as a public health problem (<1 case per 1 million population).

These targets help frame TB control; yet therein lies the very problem: the world has for too long accepted anemic efforts to merely control TB, rather than truly fight it. Why are we accepting a target of anything less than zero deaths for the next 40 years, for a disease that is both preventable and curable? What if we fall short of these inadequate targets? This is frighteningly likely, given the lack of political will to fight TB. Strikingly, the WHO’s Stop TB Strategy does not even include increasing political will in its six principal components.
Getting to Zero—Join the Movement!

By Colleen Daniels

Tuberculosis (TB), a 40,000-year-old disease, still devastates communities although it has been preventable—and curable—for decades. In 2010, the World Health Organization (WHO) reported 8.8 million TB cases—1.4 million of them fatal—worldwide. TB is the leading cause of death among people living with HIV; in 2010, it claimed 350,000 lives.

TB continues to spread: each year, one-third of all cases—or 3 million people—go undiagnosed and untreated. In 2010, there were 650,000 cases of multidrug-resistant TB (MDR-TB), which is difficult to cure; 9% were extensively drug resistant TB (XDR-TB), which is often incurable.

Mediocre efforts to reach unambitious targets delay progress in the fight against TB. The nearly 9 million people per year who fall ill with TB, and the 2 billion more who are infected with the TB bacterium and therefore at risk of developing TB disease, cannot wait until 2050 to have their well-being prioritized.

In May 2012, a group of activists, researchers, clinicians, implementers, policy makers, and foundation and government staff working to stop TB met in Cambridge, Massachusetts. During their three-day meeting, the group gave birth to a global TB strategy focused on a new target: zero TB deaths, zero new TB infections, and zero TB suffering and stigma. To this end, they created the Zero Declaration (available at http://www.treatmentactiongroup.org/tb/advocacy/zero-declaration), which has already been signed by 500 institutions and individuals.

The Zero Declaration is founded on three key realities:

1. TB is preventable and curable.
2. The main driver of today’s unnecessary TB deaths, new TB infections, and suffering and stigma is lack of political will.
3. Every country in the world has the potential to reach the goal of zero TB deaths, zero new TB infections, and zero TB suffering and stigma.

The new campaign calls for “global action and a new global attitude in the fight against TB.” Political will is essential for getting to zero; signatories called for a commitment to remedy the “global health and economic disparities that fuel the spread of TB worldwide.” In particular, political will and commitments that span beyond election cycles are needed to:

- Implement universal access to high-quality testing, care, and treatment for TB, since medications that can cure 8.2 million people are already available; and
- Increase investment in TB research and development to discover and develop new diagnostic tools, drugs, and vaccines to eliminate TB; each year, US$2 billion is needed, yet the global contribution is less than a third of the total needed.

Over the next decade, we can transform the TB epidemic. Instead of witnessing millions of unnecessary deaths, and the continuing spread of TB that is resistant to many—or all—current medications, we can get to zero.

Adequate resources will facilitate discovery, development, and implementation of affordable, easy-to-use and accurate point-of-care diagnostics for all forms of TB disease (pulmonary, extrapulmonary, pediatric, and cases in people living with HIV); vaccines to prevent TB (including cases in people living with HIV, which the current vaccine cannot); and shorter, simpler, less toxic drug regimens effective against all types of TB, including XDR-TB.

The Zero Declaration is a call to galvanize people to take action, and to work together to develop a new global plan now, instead of waiting until 2050 to eradicate TB. Sign the Zero Declaration!

GeneXpert Rapid TB Test Price Reduced in Historic Agreement

by Coco Jervis

After months of political wrangling, in early July 2012, an agreement to reduce the price of the GeneXpert MTB/RIF rapid test for tuberculosis (TB) was reached between the manufacturer, Cepheid, and pooled purchasers UNITAID, the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR), the United States Agency for International Development (USAID), and the Bill & Melinda Gates Foundation. GeneXpert was co-developed by Cepheid, the Foundation for Innovative New Diagnostics (FIND), and the University of Medicine and Dentistry of New Jersey (UNMDJ). It accurately diagnoses both TB and some common rifampin drug-resistance mutations within two hours. The Xpert molecular diagnostic system represents a major advance over microscopy, which has been the primary method of diagnosing TB for the last 125 years. The multi-stakeholder agreement represents the first in what should be a series of steps to accelerate market entry of the Xpert system. But the cost of the machines and cartridges remains high, and the lack of private-sector access greatly limits both the reach and impact of this historic agreement.

The agreement reduced the cost of individual Xpert cartridges by 40%, from US$16.98 to US$9.98 and froze the price from further increases until 2022. However, the price reduction for the cartridges will be applicable only to a set number of pre-approved public-sector purchasers in resource-poor countries with high burdens of multidrug-resistant TB (MDR-TB) and TB/HIV coinfection. Middle-income countries in Eastern Europe and Asia with high TB burdens are currently excluded from this agreement. Moreover, the price of the diagnostic system itself is still unacceptably high at US$17,000 per device. Additional costs associated with recalibrating the machine make it unattainable in many TB-affected settings.

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Widespread use of the Xpert test, which was endorsed by the World Health Organization in December 2010, could revolutionize the world’s fight against TB, as the test reduces the time to diagnosis for TB or suspected MDR-TB to two hours, from the weeks it takes for the standard TB culture to grow. As Mark Harrington, executive director of Treatment Action Group (TAG) and a longstanding TB activist, has noted, people with TB/HIV and MDR-TB are among those at greatest risk of death from TB. Delayed—or inaccurate—diagnosis costs millions of dollars in undiagnosed or improperly treated TB, which sickened more than 8 million people and killed almost 1.4 million in 2010.

This collaborative market intervention is laudable, but more needs to be done to increase access to the GeneXpert system. Further reductions in cartridge prices will be needed to maximize access to the test. TAG and our allies are calling on Cepheid to drastically reduce the price of the system itself to help ensure availability in resource-poor countries that are the hardest hit. Additionally, a tiered pricing system must be brokered that would enable private-sector providers in TB-endemic settings, as well as in middle-income countries, to have access to the system. Finally, a strategy to decentralize access to Xpert with more systemic integration into public health facilities on the ground is desperately needed. Over the past year, TAG has been working diligently with advocates to reduce the price of cartridges and to expand research advocacy and access for a point-of-care, rapid diagnostic for TB as part of the Zero Declaration (see page 11). •

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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.