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tagline

TAG
Treatment Action Group

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

Advancing Research, Securing Access

By Mark Harrington

Now in its 20th year of publication, *TAGline* has long sought to inform its readers and TAG supporters of the myriad research and policy challenges we face as a community in the ongoing fight against HIV and two of its insidious comorbidities, viral hepatitis and tuberculosis. Many of these challenges are inextricably intertwined, as we highlight in this issue focusing on specific clinical research and treatment-access hurdles threatening progress for all three diseases.

We begin with Coco Jervis's update on the Ryan White CARE Act, imperiled by political and budget paralysis in Washington, D.C., but widely considered a vital safety net for people with HIV, particularly in states with uneven implementation of the Affordable Care Act and its Medicaid-expansion provision.

INSIDE THIS ISSUE

In the expansive arena of hepatitis C drug development, we learn from Tracy Swan that pharmaceutical companies are jostling for what they hope is a billion-dollar market, merging and purging various combinations in an unseemly rush for FDA approval. Critical research and access issues remain, however.

When it comes to pediatric TB, drug companies couldn't be less interested. As Polly Clayden notes, drug- and regimen development for pediatric TB progresses even more slowly than for adult TB, and public-sector alternatives are needed to fund essential clinical trials. Meanwhile, as Lindsay McKenna explains, adaptive clinical-trial designs may allow for the rapid evaluation of new preventive and curative regimens for both pediatric and adult TB. As Erica Lessem writes, however, the high price of drugs—notably Sanofi's rifapentine—is preventing the full benefits of these scientific advances from being realized.

Over the past year, TAG has looked back to the epidemic's early, dark years, when no effective HIV treatment strategies existed. In this issue, I cover the emergence of highly active antiretroviral therapy (HAART) in 1995–96, and the vital role activists, such as TAG's Spencer Cox (1968–2012), played in demanding higher standards from clinical trials, sponsors, and regulators.

A number of highly effective antiretrovirals are coming off patent over the next five years, which could translate into billions of dollars saved for the U.S. health care system alone. But, as Tim Horn writes, we need to ensure that the best drugs and combinations are made available quickly.

Finally, HAART alone does not restore effective immunity in some 10% to 15% of people with HIV. Richard Jefferys explains that these individuals, known as immunologic nonresponders, may need additional, possibly immune-based, therapy to fully recover functional immune systems.

As it has done since 1992, TAG will continue its push for the evidence-based research required to address today's HIV, viral hepatitis, and TB priorities, and importantly, to translate the results into clinical practice as quickly as possible.

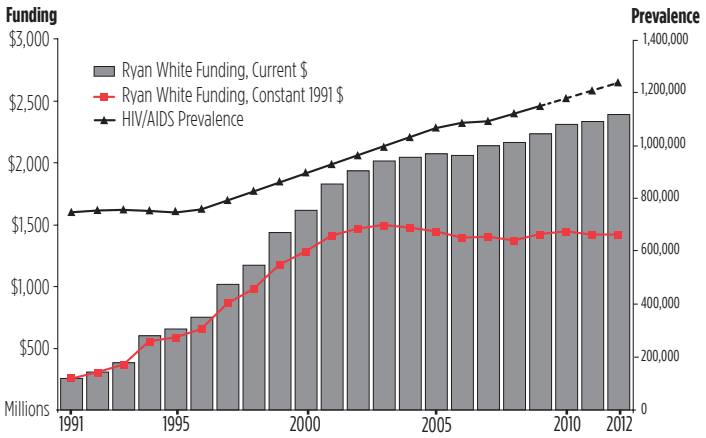
Ryan White at a Crossroads

Preparing to defend and reshape a still-critical program

By Coco Jervis

An increasing demand for services, coupled with significant fiscal retrenchment among federal and state agencies, leaves the Ryan White HIV/AIDS CARE Act-funded program at a crossroads. But advocacy strategies are afoot, not only to work toward continuation of Ryan White funding past its September 30 expiration, but also to promote a long-overdue implementation-science agenda to maximize the effectiveness and efficiency of HIV services.

Since its inception in 1990, the Ryan White program has been the "payer of last resort" for hundreds of thousands of low-income people living with HIV/AIDS in the U.S. Over the years, Ryan White–funded organizations have trailblazed the patient-centered medical-home model by integrating expert HIV medical care coordination with innovative psychosocial and supportive programs, such as housing, transportation, and meals.



Federal Ryan White funding adjusted for inflation (constant 1991 $). The Consumer Price Index (CPI) from the Bureau of Labor Statistics (BLS) was used to adjust for inflation.
Reproduced with permission of the Henry J. Kaiser Family Foundation

Given the ongoing congressional budget battles and deepening, polarizing debate on social programs and entitlement spending, many advocates are wary about pushing for a full-fledged reauthorization this year. Alternatively, since the last reauthorization bill does not have a sunset clause (a provision indicating that the CARE Act will cease unless legislative action is taken to extend the law) some advocates are pushing for a much quieter process—simply extending funding for Ryan White activities through the regular budget and appropriations process. However, this strategy may also be problematic in this fiscal climate, as funding for the program has already failed to keep pace with inflation and the increased need for services over the last decade (see figure).

Additionally, the pressure is on Ryan White organizations to adjust to a changing health care service- and delivery market. For those in states where governors have opted for Medicaid expansion, the task will be to remain relevant in places where more people will have access to insurance coverage. This may mean focusing on people with HIV who remain underinsured and uninsurable (e.g., undocumented immigrants) and expanding services beyond HIV/AIDS. Conversely, the working poor in states whose governors have opted out of Medicaid expansion will be worse off than they are now, as they will likely be ineligible for Medicaid or subsidized private insurance. This situation will undoubtedly exacerbate persisting ethnic, racial, and geographical disparities in the HIV epidemic, but it will also bring political immediacy to the dire need to expand Ryan White funding for essential wraparound prevention, treatment, care, and supportive services in those areas.

Over the course of this year, TAG staff will be looking at some of the key structural drivers of the HIV epidemic to make the case for increased research to promote better prevention, care, and service-delivery models. We are working with federal and state advocates to identify gaps in the National HIV/AIDS Strategy, Affordable Care Act implementation, and Ryan White program to expand and safeguard access to medical care for all Americans living with HIV in the coming years. •

THE G WORD
Gilead's greed gives rise to a slew of advocacy priorities

By Tracy Swan

Activists are decrying Gilead's refusal to continue codeveloping a winning HCV drug combination with Bristol-Myers Squibb (BMS), opting instead to focus on co-formulations of its own promising agents. While a high-level petition continues to circulate, demanding that Gilead continue codevelopment with BMS, a much larger advocacy agenda remains to be addressed.

The imbroglio began with the completion of a phase IIa study involving Pharmasset's nucleotide polymerase inhibitor sofosbuvir (PSI-7977) and BMS's NS5A inhibitor daclatasvir. In the absence of pegylated interferon and ribavirin, cure rates were an astonishing 100 percent after 12 or 24 weeks of treatment for people with HCV genotype 1, and between 88 and 100 percent of people with HCV genotypes 2 and 3.

Meanwhile, Gilead purchased Pharmasset for almost $11 billion in January 2012. But instead of advancing the sofosbuvir/daclatasvir regimen into phase III studies, Gilead abandoned daclatasvir in favor of developing a fixed-dose combination (FDC) with its own NS5A inhibitor, ledipasvir (GS-5885).

Gilead's FDC performed well in a phase II trial—100 percent of 25 previously untreated people and 9 null responders maintained undetectable HCV after 12 weeks of treatment—but ribavirin was included in the mix. Whether Gilead's FDC works this well without ribavirin is currently being explored in phase III studies.

Gilead's decision—should it also abandon another promising collaboration with Janssen Therapeutics, community opinion may be further soured—makes the company a tempting (and deserving) target.

A petition demanding President Obama broker ongoing collaboration between Gilead and BMS has found a wide audience. But a campaign against Gilead should broaden the focus from pre-approval trials to providing real-world access, by tackling these issues:

Pricing. Charging exorbitant prices for lifesaving drugs will limit access far more than a company's refusal to continue a codevelopment plan. By the end of 2013, sofosbuvir, daclatasvir, and Janssen's protease inhibitor simeprevir are likely to be approved—all expected to be the costliest HCV drugs to date. It is likely that that these drugs will be combined. But payers may balk, in the absence of phase III trials confirming their combined efficacy, and refuse reimbursement. Advocacy efforts to identify and target public and private insurance companies who refuse to cover these combos are likely to save more lives than demanding a pre-approval trial.

Early access. Some people cannot wait until approval—they need HCV treatment now. TAG has been advocating with allies in the U.S. and Europe for trials involving people with advanced liver disease who are ineligible for studies currently required by regulatory agencies. These "early access" trials may be lifesaving, and will provide critical information on safety and efficacy in people who need treatment most.

Inclusive trials. Gilead is moving its FDC to market as quickly as possible. There is no information on safety, efficacy, and tolerability of sofosbuvir plus an NS5A inhibitor in people with HIV/HCV coinfection, cirrhosis, or renal impairment—but these are the people most likely to use the FDC. It is to Gilead's advantage to support trials in these populations with the FDC and sofosbuvir-based combinations with drugs from other companies. •

TB Drugs for Children

Poor treatment options spur innovative research strategies

By Polly Clayden, HIV i-Base

There is an old adage in pediatric medicine: children are not little adults. This is particularly true when it comes to tuberculosis, for which management strategies are largely the same, but dosing guidance and options leave a lot to be desired. Fortunately, a number of initiatives hope to remedy this situation in an effort to reduce global TB mortality among children—currently 100,000 deaths each year.

Advances for adults have ambled over several decades and appropriate drug regimens for TB in children have lagged even further behind. As well as being hard to diagnose, children with TB are usually not infectious—meaning they are rarely considered to be a public health priority. Where children's needs are not neglected, treatment practice is mostly guided by findings extrapolated from adult research, and so may be inappropriate.

Pharmacokinetics (PK) of all drugs can vary hugely between children and adults because of physiological differences, immaturity of enzyme systems and other mechanisms involved in drug metabolism. There is also great variability across different age groups (see figure).

For treating TB, young children who are unable to swallow tablets need child-friendly formulations. Ideally these should be in solid fixed-dose combination (FDC) forms that are dispersible in liquids and can facilitate dosages across different weight groups.

Pediatric Drug Development Considerations: Pharmacokinetics

ABSORPTION

- Gastric pH higher (less acidic); by 3 years, acid per kg of body weight similar to adults
- Gastric emptying is slowed; reaches adult levels in 6–8 months

METABOLISM

- Liver immature; does not produce enough microsomal enzymes
- Older children may have increased metabolism, requiring higher dosing

EXCRETION

- Kidney immaturity affects glomerular filtration rate and tubular secretion
- Decreased perfusion rate of the kidneys
- Renal clearance reaches adult values after 2 years

DISTRIBUTION

- Total body water (TBW) 70% to 80% in full-term infants, 85% in premature newborns, 64% in children 1 to 12 years, similar to adults (greater TBW means fat content is lower)
- Decreased level of protein binding
- Immature blood-brain barrier

While scaled-down FDCs using weight-based ratios are available, the World Health Organization (WHO) revised its dosing recommendations for first-line drugs for children in 2010, after several PK studies found suboptimal levels with previously recommended dosages. This means that children are currently treated with far-from-simple mixes of FDCs and divided or single tablets to make up the dosing shortfall. This is not ideal for programs, health workers, or families.

For children who are coinfected with HIV, first-line TB treatment becomes even more complex due to drug-drug interactions between rifampicin and many antiretrovirals (ARVs).

The situation with second-line TB drugs is worse still. There are virtually no data to guide pediatric dosing. Child-friendly formulations are not usually available, and dosages using divided and/or crushed tablets are uncertain. Also, second-line drugs are more toxic than those used in first-line treatment, and adverse events are hard to monitor in children.

For prevention, isoniazid is recommended prophylaxis for TB-exposed infants. However, there are limited data to guide its dosing in neonates and low-birth-weight infants.

What is being done and needs to be done?

Although the current situation for children is a bit bleak, several initiatives, both proposed and ongoing, might offer some improvements in the not-too-distant future.

- New FDCs for first-line treatment are an urgent priority, as are strategies to use them with concomitant HIV treatment. The Global Fund and UNITAID have issued an invitation to manufacturers of TB drugs to submit an Expression of Interest for product evaluation. The generic manufacturer Svizera is developing an FDC using the new WHO dosages. A proposed trial sponsored by the U.K. Medical Research Council (MRC) will look at these, including strategies for children receiving ARVs. They will also see if treatment can be shortened from six to four months.
- For second-line treatment, the University of Stellenbosch, Cape Town, is conducting a large, five-year study to evaluate PK and toxicity of drugs for the treatment and prevention of drug-resistant TB in HIV-positive and -negative children.
- Bedaquiline, recently approved by the FDA for adults, and delamanid, will also need to be formulated and approved for children. Since 2007, all drugs under investigation for adults must have a pediatric investigation plan in order to obtain adult approval from the European Medicines Agency (EMA). The U.S. Food and Drug Administration (FDA) also offers incentives to ensure that pediatric drugs are developed. Importantly, manufacturers must ensure that drugs are submitted to regulators in low- and middle-income countries with a high burden of TB, not just in high-income countries.
- The TB Alliance has proposed a novel approach for speeding access to new TB drugs and regimens in infants and young children. Instead of the traditional approach, which involves sequential PK and safety evaluations in children (from oldest to youngest), the TB Alliance calls for single-dose PK evaluations in hospitalized TB patients in all age groups—both the FDA and EMA are, apparently, open to considering this research strategy. This approach means that approval for the youngest children would not be delayed. It is important, though, that studying the older groups is not delayed if pediatric formulations are unavailable for the younger ones.
- For prevention, the Stellenbosch group has found that isoniazid dosed at 10 mg/kg/day in low-birth-weight TB-exposed infants achieved adult target values. It noted though that the upper range of the WHO-recommended dose (15 mg/kg/day) of isoniazid might be too high for this population.

In order for us to achieve zero TB deaths and suffering in children, TB treatment activists need to understand and highlight these issues in our demands to developers, manufacturers, regulators, and other stakeholders. •

Razing the House of Cards

The discovery of HAART and the push for evidence-based HIV treatment

By Mark Harrington

The approval of therapies based on inadequate, ambiguous, uninterpretable or incomplete data offers severe and potentially insurmountable difficulties in the future evaluation of new treatments. This is the deck with which the current therapeutic house of cards was built.

—Spencer Cox, Testimony before the FDA Antiviral Drugs Advisory Committee regarding accelerated approval of stavudine (d4T), May 20, 1994

This is the third 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. In Part II: TAG's response to bad drugs, badly designed clinical trials, and inadequate surrogate markers. Here we look at the rise of highly active antiretroviral therapy (HAART) and the push for evidence-based HIV treatment.

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

Soon after its approval by the FDA in March 1987, it became clear that the benefits of zidovudine (AZT) were transient, limited by severe anemia and other toxicities, and that treatment failure was associated with the emergence of HIV resistant to the drug. Thus, even in 1989, it seemed obvious to Burroughs Wellcome's leading virologist, David Barry, who led the AZT development team, that, "You're going to have four or five drugs for the OIs and two, three and maybe four drugs for antivirals."

Dr. Barry's prediction was right, and a number of companies began fortifying their pipelines. Manufacturers either bought potential HIV agents, as did Bristol-Myers with didanosine (ddI) and Hoffmann-La Roche with zalcitabine (ddC); licensed them, as Bristol did with d4T; or set out to modify existing renin inhibitors (a class of blood pressure medications industry was attempting to develop from the 1970s on) to develop aspartic protease inhibitors (PIs), which could bind and inhibit the protease enzyme of HIV-1. Researchers from a number of companies including Abbott, Merck, and Roche began efforts to crystallize the HIV-1 protease enzyme and to screen compounds that blocked its activity, as did the National Cancer Institute (NCI).

Early in 1990, I remember gazing in wonder at a giant model of the crystallized protease enzyme published by the NCI in 1989, with little sense of whether its therapeutic promise as a target was likelier to become science or science fiction. The first PI wouldn't be approved until late 1995. We'll never know whether a sensible, directed research approach—if that isn't itself an oxymoron—could have accelerated this discovery.

By summer 1994, TAG and allies such as David Barr and Derek Link at GMHC and activist Carlton Hogan from the University of Minnesota clinical trials coordinating center had come to believe that a new approach to AIDS clinical trials was necessary, one that allowed flexibility in the control arm (participants could take whatever approved or parallel-track HIV drug they wanted) but that restored rigor to the process by randomizing participants to receive a new PI or a placebo at a 2:1 ratio—and that used clinical endpoints, notably time to an AIDS-defining event or death—rather than relying on the discredited surrogate marker of CD4 cell count changes due to therapy.

We then released our report, *Rescuing Accelerated Approval: Moving Beyond the Status Quo*, which was distributed at a contentious FDA advisory committee hearing in September 1994 (reviewed in "On a Darkling Plain" in the October 2012 *TAGline*).

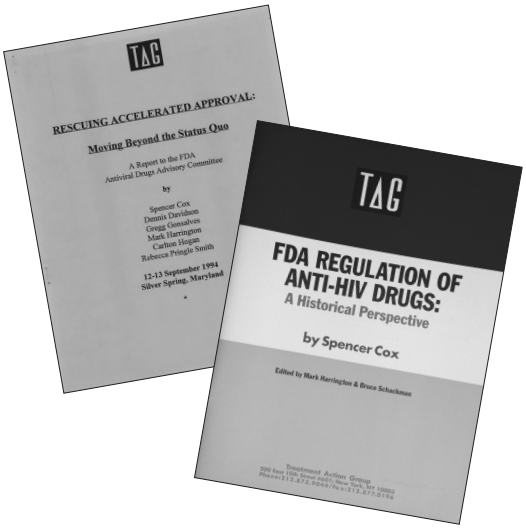
TAG and our allies worked assiduously to watchdog the phase II/III clinical trials of every company that was making an HIV PI, including Abbott's ritonavir, Agouron's nelfinavir, Merck's indinavir, and Roche's saquinavir. TAG's recommendations to regulators and companies were published in the February 1995 report *Problems with Protease Inhibitor Development Plans*.

In summer 1995, Spencer Cox published his scathing, still-compelling report, *FDA Regulation of Anti-HIV Drugs: A Historical Perspective*—a cautionary retrospective on the first, mostly unsuccessful, ten years of HIV drug development and regulation.

Drug Combinations to the Fore

In September 1995, Spencer Cox, Michael Marco, Tim Horn, and I attended the 35th ICAAC, where the results of AIDS Clinical Trials Group study 175 were presented, along with early phase I viral-load data from Abbott's ritonavir development program.

ACTG 175 was the first study to prove, using clinical endpoints, that ddI alone, AZT + ddI, or AZT + ddC were better than AZT alone, in both AZT-naive and -experienced persons, in terms of slowing progression to AIDS or death.



"I mean, it's not like I live for bad news. It looks like we're making some progress," commented Spencer Cox in *TAG Does ICAAC*.

An early Abbott study of ritonavir + AZT + ddC appeared to show even more arresting data: According to lead author Daniel Norbeck, the regimen yielded a CD4 count increase of 110 cells and an unprecedented 2.5 log decrease in viral RNA lasting for the 20 weeks of the study. Over the subsequent weeks, Norbeck claimed, an increasing proportion of participants became viral culture–negative—which is to say they could not culture infected cells from the blood.

The era of monotherapy was on its way out.

In November 1995, the FDA advisory committee met to review Roche's application for accelerated approval of saquinavir, Glaxo Wellcome's for accelerated approval of lamivudine (3TC), and Bristol-Myers's for full approval of stavudine (d4T). The three-day hearing was neither pleasant nor terribly informative. Moving to the combination-therapy era without the proper monitoring tools—e.g., quantitative viral-load testing, which came

of age only the following year—made it difficult to assess the benefit of the two AZT-like drugs and that of the first PI, saquinavir.

Nonetheless, we believed that Roche had met our demands from the previous year, notably: adequate and well-controlled clinical endpoints studies were under way to show whether the drug could prolong disease-free time or survival; the completion or implementation of studies to demonstrate a favorable combination of changes in CD4 levels and viral load; evidence adequately characterized and acceptable safety evidence; and efforts to enroll an expanded access program.

Therefore, we supported approval of saquinavir, despite its low dose and the lack of definitive clinical endpoint data. The drug was approved in December 1995. Less than two years later, Roche admitted that the licensed dose was suboptimal, though it didn't take responsibility for exposing people to a greater risk of cross-resistance to other, more potent PIs. Ultimately, Roche developed a more bioavailable dose that could have competed with the stronger PIs, but it was too late; the drug was doomed by the company's early mistakes.

Luckily, the FDA had taken proactive steps to expedite its review of the next two PIs in the pipeline, both of them more potent than saquinavir: Abbott's ritonavir and Merck's indinavir.

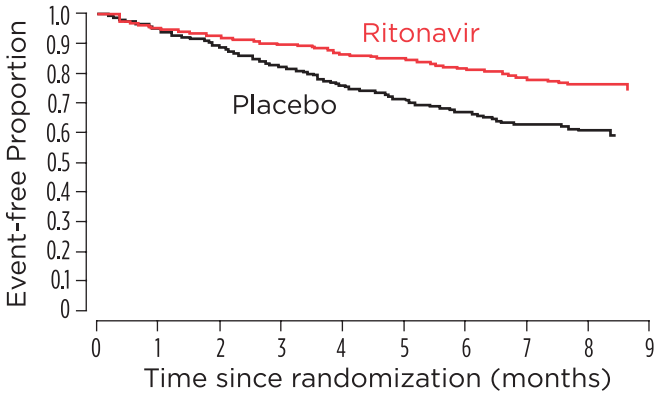
Abbott had adopted Spencer Cox's recommendation (from the 1994 *Rescuing Accelerated Approval: Moving Beyond the Status Quo* report):

> *After discussing the proposed expanded access program "for people who have failed or proven intolerant to all available AIDS drugs, or who have under 50 T-cells, TAG proposes a standard expanded access program, in which all patients would receive protease inhibitor, but would be randomly assigned to either high-dose or low-dose...*

> *For other people with HIV, TAG has proposed a 'large, simple trial.' Essentially, all HIV-positive people would be eligible for participation, with those above and below 200 T-cells studied separately. Study participants would be randomly assigned to take either one of two protease inhibitors or placebo, or one of two different protease products and placebo. Other than their study treatment, participants would be able to take any other drug they wanted, approved or unapproved, and to pursue the best medical care...*

Annus Mirabilis

On February 1, 1996, at the 3rd Conference on Retroviruses and Opportunistic Infections in Washington, D.C., Abbott showed the results of the ritonavir study. In just six months, those receiving ritonavir + standard of care (SOC) had 50% fewer deaths than those receiving placebo + SOC. Spencer, attending CROI, was in tears: "We're going to live!" (see figure).



Evidence of survival with a protease inhibitor. A Kaplan-Meier analysis demonstrating the proportion of subjects who survived and remained free of a new AIDS-defining diagnosis while being treated with either ritonavir or placebo. Adapted from Cameron et al. Lancet. 1998 Feb 21;351(9102):543–9.

On February 29, 1996, the FDA advisory committee reviewed ritonavir. Spencer Cox was the ad hoc community representative on the panel. The committee resoundingly recommended approval. On March 1, 1996, the FDA approved ritonavir. Merck's indinavir was approved two weeks later, Roche's Amplicor-brand RT-PCR test for HIV RNA was approved three months later, and on June 21, the FDA granted accelerated approval to the first-ever non-nucleoside reverse transcriptase inhibitor, Boehringer Ingelheim's nevirapine (Viramune).

The media became a bit giddy. At the end of June, the *Economist* cover story read: "A Solution for AIDS?"

Everything culminated at the 11th International AIDS Conference in Vancouver, British Columbia, in early July 1996. John Mellors presented his famous paper from the Multicenter AIDS Cohort Study (MACS) showing that viral load predicted the rate of CD4 decline. Virologist John Coffin delivered his famous metaphor comparing the HIV-infected patient to a train speeding along a track towards a deadly cliff—the viral load conveying the speed of the train, with CD4 count measuring the distance to the cliff.

On July 11, 1996, the last day's latebreaker presentations confirmed the overwhelming and unexpected benefit of triple-combination therapy when initiated simultaneously in people who had never received the drugs in question. Six researchers from four teams showed results from six studies of five different regimens that reduced HIV RNA levels to undetectable levels in the plasma.

One of the most dramatic presentations was made by David Ho of the Aaron Diamond AIDS Research Center (ADARC), presenting on 12 antiretroviral-naive individuals receiving AZT/3TC/nelfinavir. CD4 counts started at 245 and viral load at 56,000. CD4 counts rose by about 100 cells, while "at twelve weeks, all eleven patients remaining on the study had levels below that threshold [25 HIV RNA copies/ml], and predicted that they were essentially at zero."

As I wrote in *Viral Load in Vancouver*:

> *The room became very quiet. You could have heard a pin drop. A collective silent sigh ensued, as the full implications of this sunk in to the thousands of scientists, reporters and activists assembled on this last late-breaker session of the Vancouver conference. People I knew and loved were in this study. Their viral load had been reduced, within three months, to virtually zero. Perhaps some of us would live, after all.*

On August 6, I went down to the NIH Clinical Center for my second lymph-node biopsy. My viral load was 76,790 (Chiron bDNA). The next day, I started my first antiretroviral treatment: 3TC/d4T/indinavir. By August 23, my viral load had dropped to 2,932 (PCR). By December, my CD4 cells had risen from 152 to 597 and viral load was undetectable.

Not everyone fared as well. Spencer Cox, who was extensively antiretroviral-experienced, mostly with nucleoside analogues, initially responded well to ritonavir but then developed resistance. In midsummer, he switched to indinavir, yet by late September his viral load was virtually back to baseline, at 400,000, just seven months after starting ritonavir. We all feared this trajectory was a harbinger of dangers that might be ahead for everyone who appeared to benefit in the short-term from triple-combination therapy.

On September 21, Tae-Wook Chun, then of Bob Siliciano's lab at Johns Hopkins, later at NIAID, lectured at ADARC on cellular latency of integrated HIV provirus in resting CD4 cells. This prefigured the end of the eradication theory put forth by David Ho and Alan Perelson earlier in the year, by which triple therapy given for a few years might cure HIV.

Two days later, we met Mike Saag from the University of Alabama at Birmingham to talk about his proposed START protocol ("Strategic Timing of ART," ACTG 355). This study would be labeled "overly ambitious" by the ACTG and withdrawn in March 1997. The ACTG would never do a "when to start" study, and 17 years later we still don't know the best time to initiate ART for individual benefit.

That fall, the Department of Health and Human Services convened a Public Health Service panel to develop clinical practice guidelines for HIV. Both Spencer Cox and I were named to the panel, which was to develop the first guidelines for the use of highly active antiretroviral therapy (HAART).

Laurie Garrett's cover story in *Newsday*, "The Curse of the Cure" rounded out the year on December 17. Spencer and I were on the cover. Which one had the drug-resistant HIV? And how long would the benefits of HAART last for anyone, drug experienced or drug naive?

At the end of the year I wrote in *TAGline*:

> *On a public health level, assuring access to and information about new treatment strategies is an enormous task even in the developed world, and the chances of extending their use to the developing world where over 90% of HIV cases occur appear slender until and unless a new global commitment to providing health care to all emerges. Given the political landscape in the USA, where even its own citizens are routinely denied access to health care, this prospect seems remote. More likely is the recapitulation with HIV of what occurred with tuberculosis, when several generations of effective drugs were wasted by inadequate public health efforts, resistance to all of them emerged, and, after a hiatus of several decades, tuberculosis returned with a vengeance in a new, multi-drug resistant form, its re-emergence amplified by the widespread immune dysfunction triggered by the HIV pandemic.* •

NEW TAG PUBLICATIONS

Funding Scientific Innovation: Global Investments in HIV Treatment Research and Development in 2010 and 2011. Our new report, produced in collaboration with AVAC, found that US$2.6 billion was invested in HIV treatment R&D in 2011 by 41 public, private, and philanthropic funders. This is a 12% increase in funding from the baseline year of 2009, with the majority of funding targeted at research for new medications. This report is available at: www.treatmentactiongroup.org/hiv.

In partnership with the Sentinel Project on Pediatric Drug-Resistant Tuberculosis, TAG has released ***We Can Heal: Prevention, Diagnosis, Treatment, Care and Support: Addressing Drug-Resistant Tuberculosis in Children***. This collection of stories of 30 children with drug-resistant tuberculosis in 30 countries underscores the need for improved programs, policies, and tools to reach the goal of zero TB deaths, new infections, and suffering.

TAG's TB/HIV Project has also released ***An Activist's Guide to Bedaquiline (Sirturo)***, highlighting the important safety and efficacy data reported thus far, along with research and access recommendations for activists to take forward. Both ***We Can Heal*** and the bedaquiline guide are available at: www.treatmentactiongroup.org/tb.

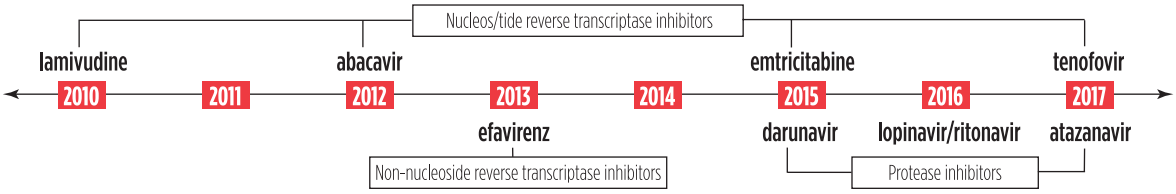
A new fact sheet, ***Hepatitis C and the IL28B Gene***, is now available for download from TAG's Hepatitis and HIV Project. IL28B is a genetic factor that helps explain responses to hepatitis C treatment, including poorer efficacy among African Americans and people of African ancestry. This fact sheet is available at: www.treatmentactiongroup.org/hcv/factsheets.

Preparing for GENERICS

The push for affordable HIV treatment doesn't end with patent expirations

By Tim Horn

Expiry of guidelines-preferred and -alternative first-line ARTs



The United States is on course for some much-needed economic relief from the crippling cost of HIV treatment, with the anticipated arrival of generic versions of guidelines-preferred antiretrovirals. However, much preparation is required to maximize price competition, maintain patient choice, and ensure that savings are used to the advantage of people living with HIV.

With the patent expiration of efavirenz sometime this year, a generic-based regimen comparable to Atripla is on the horizon: efavirenz combined with lamivudine and branded tenofovir (Viread). According to recent mathematical modeling conducted by Rochelle Walensky of Harvard Medical School and colleagues, the U.S. health care system savings associated with this regimen could be up to $560 million in the first year alone; a regimen containing three generics would save up to $920 million.

The study has stirred up a much-needed dialogue on coming generics, but it has also come under criticism for its projection of reduced efficacy using efavirenz/lamivudine/Viread: a switch could shorten life expectancy by 4.4 months. The model based this projection on data showing lamivudine to be not as potent as emtricitabine in Atripla, though a recent analysis by the World Health Organization suggests this is likely unfounded, particularly when powerful agents like efavirenz and tenofovir are used. Another concern is that a switch from a single-tablet regimen to a three-tablet (albeit once-daily) regimen will affect adherence, yet as Médecins Sans Frontières (MSF) and others have noted, there are surprisingly few data to confirm this hypothesis.

Recognizing that fixed-dose combination (FDC) tablets are a preference, compounded by the reality that a three-tablet regimen may yield insurance copayments that exceed those for branded FDCs, a concerted advocacy effort will be required to push for the import and/or development of FDCs containing, at least initially, generic efavirenz and lamivudine plus branded tenofovir and, eventually, a repertoire of single-tablet offerings as other patents expire in the coming years (see figure).

For cost savings to occur, competition among generic manufacturers will be required. Walensky's projections are based on 75% price reductions—an assumption based on competitive cost-cutting seen when non-HIV drugs become available generically. To achieve this, policies such as mandatory generic substitutions may increasingly become the norm.

Though it is only through market competition that drug pricing would no longer be determined only by what the market will bear but also by what it can sustain, activists need to ensure that patient and provider choice of treatment options is not unduly restricted as a result.

Lastly, we need to ensure that any savings are reinvested in HIV. With roughly one-third of people with HIV in regular care and only one in four being effectively treated, redirecting funds for testing, linkage-to-care, and retention efforts has never been needed more. •

Undetectable Is Not Always Enough

Immunologic nonresponders face increased risk of illness, but lack therapeutic options

By Richard Jefferys

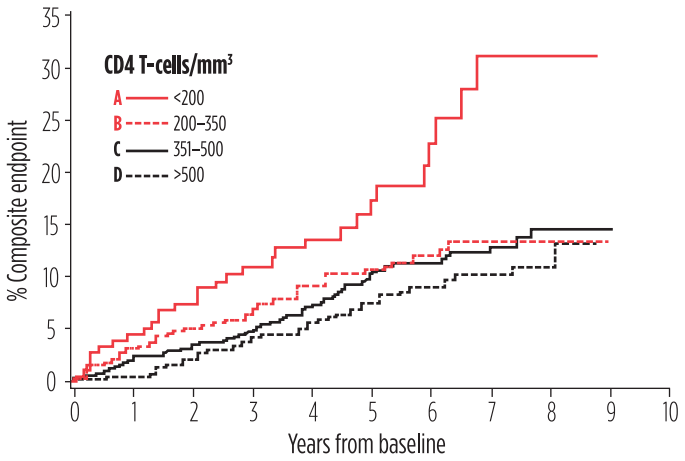
A subset of people on antiretroviral therapy (ART) experience limited or no recovery of CD4 T-cell counts despite achieving and maintaining undetectable viral loads. Various terms have been used to describe this phenomenon, with the most common being "immunological nonresponders" (INRs). Many studies have documented that INRs face an increased risk of illness and death compared with people with more robust CD4 T-cell gains. Yet there are no approved therapies to improve immune reconstitution, and clinical trials of potential candidates remain few and far between.

Approximately 5–10% of individuals initiating ART have been characterized as INRs, usually based on minimal change from baseline levels or failure to reach a threshold (e.g., 350 cells) after several years of viral suppression. The most prominent risk factors are a low CD4 T-cell count at ART initiation and older age.

A number of biological mechanisms that contribute to inadequate CD4 T-cell recovery in INRs have been identified. These include compromised production of CD4 T cells (and other lymphocytes) in the bone marrow and reduced output of T cells from the thymus. Both bone marrow and thymus function also decline naturally with age, likely explaining why older age is a risk factor.

CD4 T-cell survival is also shortened in INRs due to heightened activation of the immune system (driving cells into a short-lived activated state) and fibrotic damage to lymph node structures that normally provide sustenance to CD4 T cells via the cytokine IL-7. Potential contributors to heightened immune activation in INRs include coinfections such as CMV and hepatitis C, and microbial translocation (the leakage of gut bacteria into the systemic circulation due to reduced immune surveillance in the intestine).

Multiple cohort studies in the Americas, Europe, and Africa have assessed clinical outcomes among INRs followed over several years. The results have been very consistent: the overall rates of illness and death among individuals with sustained HIV suppression are relatively low, but the risk of both AIDS- and non-AIDS-related events is significantly increased compared to individuals with superior CD4 T-cell count recovery (see figure).



Poor CD4 T-cell recovery, despite suppression of viral load, was associated with an increased risk of death, AIDS, cancer, liver disease, and cardiovascular events (composite endpoint) in the Dutch ATHENA HIV cohort. Compared with Group A, Group D had a 46% reduced risk of the composite endpoint. Group B had a 66% reduced risk of the composite endpoint. Adapted from van Lelyveld et al. AIDS. 2012 Feb 20;26(4):465-474.

These findings jibe with those from analyses showing that individuals on ART who achieve CD4 T-cell counts over 500 show mortality relates comparable to uninfected individuals, while those who do not continue to face a shortfall in life expectancy.

So far only one large-scale trial (named SILCAAT) has tested whether an adjunctive therapy can reduce illness and death among INRs on ART. The study started in 1999 and tested IL-2, a cytokine that had been shown to stimulate CD4 T-cell proliferation, but it failed to show any clinical benefits. Subsequent analyses revealed that IL-2 preferentially increased numbers of a type of immune-suppressive regulatory CD4 T cell, emphasizing that not all CD4 T cells are created equal, and that the mechanism of action of an immune-based therapy can be crucial to whether it confers improvements in health.

An array of small studies have explored the immunologic effects of other possible therapeutic candidates; among those that have fallen by the wayside are the CCR5 inhibitor maraviroc and a putative thymus-enhancer named keratinocyte growth factor. Human growth hormone (HGH) looked promising in one trial, boosting thymus volume and CD4 T-cell production, but is widely viewed as having too many potentially serious side effects to be worthy of further consideration.

Among the candidates that appear to have most promise are Sangamo BioSciences' SB-728-T gene therapy, which involves extracting CD4 T cells from individuals, modifying them in the laboratory to abrogate expression of the HIV coreceptor CCR5, then expanding and reinfusing them. Phase I studies in INRs reported sustained CD4 T-cell count increases, unprecedented improvements in CD4 to CD8 T-cell ratios, and anecdotal evidence of clinical benefits. However, the company is now focused on trials aiming to achieve a functional cure of HIV infection and does not appear interested in pursuing further trials for INRs (those in the phase I study have also been denied additional rounds of infusions of gene-modified CD4 T cells, due to a claim of limited resources on the part of the company).

A group of Chinese scientists has recently published evidence that mesenchymal stem cells, which are obtained from donated umbilical cords, can significantly improve immune reconstitution and reduce immune activation in at least a subset of INRs; they are now conducting expanded studies.

Currently, the lead candidate for clinical evaluation is the cytokine IL-7, which has produced sustained increases in T-cell counts in several trials (including gut CD4 T-cell numbers), with a recent analyses also suggesting these increases are associated with declines in inflammatory biomarkers and CD4 T-cell activation. IL-7's mechanism of action differs significantly from IL-2's, and it lacks the latter's notorious flu-like side effects and the bias toward inducing regulatory CD4 T cells. The manufacturer, a small Parisian Biotech company named Cytheris, is now planning a phase III trial to assess clinical outcomes among INRs.

A search of the clinicaltrials.gov database indicates that there are five studies of interventions for INRs, only one of which is in the United States (a trial of two nutritional supplements, zinc and S-adenosylmethionine [SAM-e], that is due to open for enrollment in Atlanta and Seattle). None is evaluating clinical endpoints.

The shift to recommending earlier ART initiation should reduce the incidence of INRs, but late diagnosis is an ongoing problem, and thus the unmet need of this population is unlikely to evanesce anytime soon. Advocacy efforts should remain cognizant of early ART's potential in this regard, while also seeking to ensure that the health benefits of candidate therapies are assessed and that additional novel approaches are identified and advanced into clinical trials. •

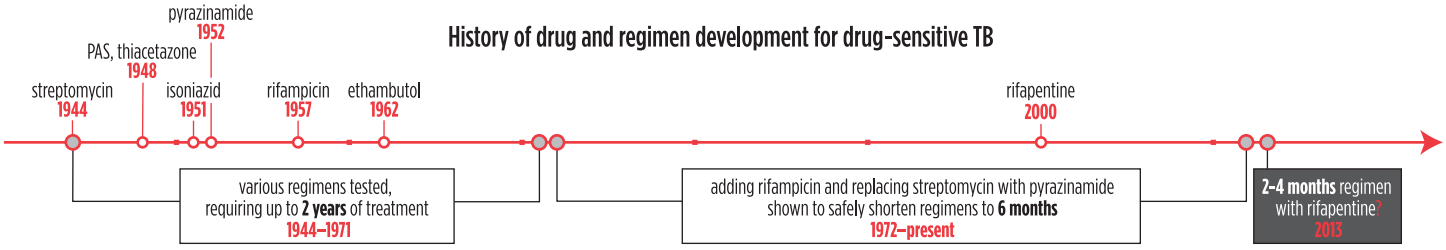
Sanofi's Double-Edged Sword

Rifapentine's manufacturer helps to advance TB research while stalling access

By Erica Lessem

Sanofi-Aventis, manufacturer of the tuberculosis (TB) drug rifapentine (Priftin), can be credited for aiding research efforts to shorten and simplify treatment dosing for TB. However, the company's pricing of the drug has hampered access to such regimens, even in resource-rich nations like the United States.

While first-line therapy for drug-sensitive TB is effective, its six-month duration and daily pill burden discourages treatment adherence and taxes health care systems. Similarly, treating latent TB infection generally requires nine months of daily treatment, meaning that many discontinue, or do not initiate. Though TB treatment has improved over time (see figure), shorter, simpler regimens for preventing and curing TB are crucial.



Adapted from Fox et al. Int J Tuberc Lung Dis. 1999 Oct;3(10 Suppl2):S231–79; Keshavjee et al. N Engl J Med. 2012 Sep 6;367(10):931–6.

Rifapentine (Priftin) is an approved drug for active TB. In the same class as rifampicin—one of the backbones of first-line TB therapy—rifapentine has a longer half-life, and may be preferable for intermittent or treatment-shortening regimens. Sanofi is collaborating with the U.S. Centers for Disease Control and Prevention's Tuberculosis Trials Consortium (TBTC), along with the International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis (INTERTB), to explore simplified latent and active TB treatment regimens.

Specifically, a TBTC study showed that using rifapentine with isoniazid could shorten latent TB treatment to just 12 once-weekly doses. Another TBTC study, and a recent INTERTB study, showed that for active TB, replacing rifampicin with rifapentine in the last four months of treatment may permit once-weekly, rather than daily, dosing. The TBTC is also developing a phase III trial to determine the potential of rifapentine to shorten active TB treatment.

Implementation of these evidence-based practices has, unfortunately, been minimal—primarily due to the drug's prohibitive pricing, compounded by major TB budget cuts. In late 2012, Sanofi lowered the U.S. federally discounted price of rifapentine from $73 to $51 per box of 32 tablets. In contrast, isoniazid costs just $0.05 per tablet. Given the potentially large market for rifapentine if the price were lowered, reductions could be cost-neutral or even lucrative for Sanofi. However, in January 2013, Sanofi rejected a request from U.S. and international TB program managers, researchers, and advocates to further lower rifapentine's price.

The 10,000 people in the U.S. alone who get TB annually, along with hundreds of thousands of infected contacts, urgently need better treatment options—as do providers, TB programs, and taxpayers. Sanofi's contributions to advance TB research are not meaningful if rifapentine is ultimately inaccessible. Removing cost barriers is critical to bridge the gap between TB research and practice. •

A Necessary Transformation

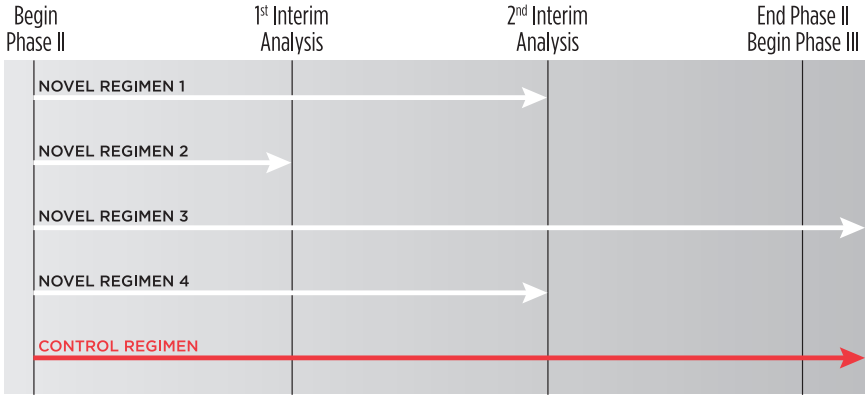
Simultaneous, not sequential, evaluations of novel drug regimens needed to speed TB treatment research

By Lindsay McKenna

New drugs, as components of novel regimens, are necessary to improve TB treatment. To expedite the development of these regimens, while simultaneously reducing the size, length, and cost of clinical trials, TB researchers, funders, and activists are working together to develop alternative study designs.

Traditional phase II studies evaluate TB regimens containing new agents sequentially—one at a time, compared with a standard control regimen—an approach that can take 20 years to yield a regimen that is desirably shorter, simpler, safer, and more effective than the existing standard of care. This process is too lengthy and expensive for the TB crisis and must be streamlined to achieve progress as fast as possible while producing rigorous data on safety and effectiveness.

Adaptive phase II clinical trials include multi-arm, multi-stage (MAMS) studies. These protocols involve simultaneous evaluation of multiple experimental regimens, using interim analyses to drop study arms deemed intolerable or ineffective based on surrogate marker data, such as time to culture conversion (see figure). The aim of such studies is to efficiently determine which novel regimens to comparatively evaluate for relapse-free cure rates in phase III trials. MAMS studies in development include the U.S. Centers for Disease Control and Prevention's Tuberculosis Trials Consortium phase II Combination Regimens for Shortening TB Treatment (CRUSH) study, and the AIDS Clinical Trials Group's MDR-Additive Regimens Varying Experimental Layouts (MARVEL) study.



An example of a multi-arm multi-stage (MAMS) phase II trial design. At the first interim analysis, novel regimen 2 is considered to lack sufficient benefit compared with the control and is not taken forward to stage 2. At the second interim analysis, recruitment to novel regimens 1 and 4 is stopped, and only the control regimen and novel regimen 3 are continued to the end of trial and advanced into phase III studies.

Adaptive designs—already being used to study regimens for hepatitis C and a variety of cancers—may expedite novel TB regimen development and optimize use of limited resources. Risks include erroneous termination of an effective and safe regimen that appears ineffective or unsafe at interim analysis, and statistical difficulties in comparing multiple arms. There is also the challenge of designing novel regimens using approved and experimental drugs with overlapping toxicities, such as heart-rhythm disturbances.

Researchers should design adaptive TB drug trials, and pharmaceutical companies must make novel drugs available in combination with other compounds in development. Furthermore, regulatory authorities need to provide clear guidance on conducting adaptive clinical trials to assure quality data and participant safety—much as the U.S. Food and Drug Administration did with the release of its draft *Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics* in February 2010.

Activists can help achieve these priorities by working with research consortia to push forward adaptive designs in a way that takes into account community priorities and concerns. We also need to encourage pharmaceutical companies to provide novel drugs for adaptive trials and petition regulatory authorities to develop clear guidance on their design and implementation to ensure that such studies are scientifically sound and ethical. •

Help Paying for HIV and Hepatitis Treatment

Health insurance co-payment (co-pay) programs and patient drug assistance programs (PAPs) are critical services for thousands of U.S. residents with HIV and/or viral hepatitis who face out-of-pocket expenses associated with their treatment. The Fair Pricing Coalition (FPC) has negotiated co-pay programs with virtually every major HIV and viral hepatitis drug manufacturer—which will continue to be essential as more people with HIV and/or hepatitis are rolled into private insurance plans with the implementation of the Affordable Care Act—and is working on expanding PAPs, particularly the eligibility criteria for those on state AIDS Drug Assistance Program (ADAP) waiting lists.

The FPC has published lists of co-pay programs and PAPs for people with HIV and hepatitis B and C. The lists include eligibility criteria and contact information for these programs. The lists will be updated as changes to programs occur. Learn more at: http://fairpricingcoalition.org/projects.

SUPPORT TAG

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

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

ABOUT TAG

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

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

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

TAG
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