Collaboration and Conflict: Looking Back at the 30-Year History of the AIDS Clinical Trials Group

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The dark brown couch—probably government-issued Naugahyde—in the office of Anthony Fauci, MD, shows its age, the edges of its square seat cushions cracked and white.

Fauci’s hair is whiter now than it was 30 years ago, when, as the newly appointed director of the National Institute of Allergy and Infectious Diseases, he invited 2 colleagues, John LaMontagne, PhD, and Maureen Myers, PhD, to sit on the couch and discuss the need for a concerted national effort to test AIDS therapies.

Discovery of the virus that causes AIDS had been announced in 1983 (Barré-Sinoussi F et al. Science. 1983;220[4599]:868-871), and by the fall of 1985, Fauci expected a flood of drugs would come through the pipeline over the next few years. “There was a precedent for clinical trial units, and that was mostly in the cancer field, but there was no precedent for the ultimate magnitude of this [undertaking],” Fauci said in a recent interview in his office on the Bethesda, Maryland, campus of the National Institutes of Health (NIH).

It was unlikely that any single trial unit would be able to enroll enough patients to reach a desired clinical end point, Fauci said. But create a network of clinical trial units, and you could pool all the data and quickly get answers.

“We were dealing with a disease that was essentially 100% fatal,” he said. “So when we were trying to determine whether a drug worked or not, we needed to know the answer right away.”

The ACTG Is Born

Myers, 72 years old, now retired and living in Carlisle, Massachusetts, recalled that she and LaMontagne were eager to start work on creating a network of AIDS clinical trial units. The same evening after their discussion with Fauci, they headed for the closest comfortable spot—Myers’ home. “I lived about a mile from the (NIH) campus, and John lived in Alexandria (Virginia),” she said. “We sat down at my dining room table and started sketching out what [the clinical trials program] would look like,” she said.

They worked into the night, laying the foundation for the AIDS Clinical Trials Group (ACTG), which supported groundbreaking research that transformed a death-sentence disease into a chronic illness that could be managed for decades with medication.

“We were so hyped,” said Myers, who still has the rosewood table on which they worked. “We just got carried away with the unbelievable undertaking we had just been asked to address.” By June 1986, the NIH had awarded contracts to 14 AIDS treatment evaluation units and added 5 more in September 1987.

The news wasn’t greeted with universal enthusiasm, however.

“There were some who criticized us… and said, ‘Why are you investing so much money in 14 units when you don’t even have any drugs?’” Fauci said. “And my response was, ‘Pretty soon we’re going to have more drugs than we’re going to be able to test, so we might as well set up the units and have them ready,’” he added. “That was actually a very good decision.”

However, some researchers bypassed working in the ACTG. “Not everyone who was interested in antivirals necessarily wanted to jump into AIDS,” Myers recalled. They were engrossed in pursuing treatments for other life-threatening infections, such as herpes encephalitis, she said.

Instead, many proposals came from physicians who already were seeing patients with AIDS, Myers noted. “[There] was a compelling need [for clinical trials]. It was hard not to get involved.”

Her collaborator, LaMontagne, died in 2004. But since that fateful conversation on Fauci’s couch, the ACTG has expanded from the 14 original US AIDS treatment evaluation units in 1986 to 62 sites currently in the United States, Canada, India, Thailand, South Africa, Kenya, Tanzania, Haiti, Malawi, Botswana, Brazil, Uganda,
and Peru, making it the largest network of therapeutic clinical trial units in the world.

**ABCs of AZT**

One of the first contracts went to the University of California, San Francisco, where cancer specialist Paul Volberding, MD, served as principal investigator of the unit. Volberding, now 66 years old and codirector of the UCSF-Gladstone Center for AIDS Research, still remembers the exact date on which he saw his first patient with AIDS: July 1, 1981.

At the time a research fellow in the virology laboratory of Jay Levy, MD, one of the first researchers to isolate HIV (Levy JA et al. Science. 1984;225[4664]:840-842), Volberding was only 31 years old, and his career took off along with the AIDS epidemic. In 1983 at San Francisco General Hospital, he helped establish the first inpatient ward for people with AIDS.

He recalls the immense pressure to develop an effective treatment. “People were dying, and all we could do was hold their hands,” recounted Volberding, who served on the ACTG executive committee and led ACTG 019, the pivotal trial that changed clinical practice by demonstrating that the antiretroviral drug AZT, or azidothymidine, was safe and effective in delaying the onset of AIDS in asymptomatic people with HIV (Volberding PA et al. N Engl J Med. 1990;322[14]:941-949).

The groundwork for ACTG 019 was set years before the trial began (Broder S. Antiviral Res. 2010;85[1]:1-18). With the help of a National Cancer Institute (NCI) grant, Wayne State University scientist Jerome Horwitz, PhD, synthesized AZT as a potential cancer therapy in 1964; it didn’t work, and he shelved it. But 20 years later, given the drug’s structure and antiviral properties in vitro, Burroughs Wellcome, the British pharmaceutical company that merged with Glaxo (now GlaxoSmithKline) in 1995, resurrected AZT. The drugmaker submitted it to the NCI, which was screening existing drug compounds in vitro in a desperate search for something that might combat HIV.

Testing at the NCI showed that AZT suppressed HIV replication in doses that did not damage normal cells, so Burroughs Wellcome funded a trial involving patients with advanced AIDS. It found that AZT decreased deaths and opportunistic infections (Fischl MA et al. N Engl J Med. 1987;317[4]:185-191) but with significant drug toxicity, the worst of which was bone marrow suppression (Richman DD et al. N Engl J Med. 1987;317[4]:192-197). In March 1987, AZT became the first drug to win US Food and Drug Administration approval for treating AIDS. By the end of that year, 50 378 cases of AIDS had been reported in the United States, and 40 849 people had died—a death rate of about 80% (http://bit.ly/IwS8kjO). But between 1990 and 2013, HIV interventions including AZT and newer antiretroviral drugs saved an estimated 19.1 million years of life worldwide (http://bit.ly/1Y6qOfa).

“It really took subsequent trials to broaden that [initial finding],” said Volberding, who is no longer affiliated with the ACTG.

Margaret Fischl, MD, at the time was a young University of Miami internist who, like Volberding, became involved with the ACTG as a result of her work with patients with AIDS. Lead author of the report on the first placebo-controlled AZT trial, Fischl also led ACTG 016—the 16th ACTG trial—which compared AZT with a placebo for patients with AIDS who weren’t as sick as those in the Burroughs Wellcome trial (Fischl MA et al. Ann Intern Med. 1990;112[10]:727-737). AZT was shown to be at least as effective as in the earlier trial but this time with little toxicity, because the daily dose had been lowered from 1500 mg to 1200 mg. Another study published the same year, also with Fischl as lead author, showed that the daily dose could be lowered to 600 mg, which further reduced toxicity without compromising efficacy (Fischl MA et al. N Engl J Med. 1990;323[15]:1009-1014).

Still, testing AZT in asymptomatic HIV-positive people was a bold step, because it wasn’t yet known if they were all destined to develop AIDS. “The idea of giving this drug to people who were still ‘healthy’ was a little bit out there,” said Volberding, who in 1989 editorialized that HIV infection itself was a disease (Volberding P. J Acquir Immune Defic Syndr. 1989;2[5]:421-425).

Many people with asymptomatic HIV infection wanted AZT, though, and it...
wasn’t easy to get outside of the trial, Volberding said. “The trial was designed and up and running in about 3 months,” he said. “It accrued like gangbusters.”

Like every other chapter of the AIDS epidemic, ACTG 019 and AZT itself were not without controversy.

“Death by placebo’ was one headline in one of the gay papers here,” Volberding recalled. And then there were the “denialists,” as he calls them, who argued that HIV did not cause AIDS, so a toxic drug to treat it was akin to murder. Instead of targeting HIV, they argued, scientists should try to strengthen the immune system.

At the 1996 International Conference on AIDS in Vancouver, protesters from the activist group ACT UP (AIDS Coalition to Unleash Power) threw fake blood on him and Fischl during a panel about combination antiretroviral therapy. “Volberding; your lies kill!” AZT’s a toxic pill!” the protesters chanted (http://bit.ly/IP43btl).

Activists and the ACTG

Probably the most vocal critic of the ACTG was Larry Kramer, the playwright and author who cofounded ACT UP and Gay Men’s Health Crisis.

“There is medicine before Larry Kramer, and there is medicine after Larry Kramer,” Fauci said, noting that ACT UP protests caused a “profound change” at the NIH in the search for cures for many diseases.

In 1988, the year a routine blood test revealed he was HIV-positive, Kramer published “An Open Letter to Dr. Anthony Fauci” in the Village Voice, which was reprinted in several other newspapers (http://bit.ly/IG3dPFS). In the piece, Kramer slammed Fauci because many of the drugs that the ACTG drug selection committee had deemed a high priority had not yet been tested.

In a 2006 PBS interview, however, Kramer described Fauci as “the only true and great hero in all of this,” in the government, in the system…. I acknowledge him every chance I can, because we certainly got off to a rocky start.” (http://to.pbs.org/L4gcY9)

But in an email to JAMA in October, the now 80-year-old Kramer was less than complimentary about ACTG. “The ACTG was a nightmare to get set up and into some sort of working order,” he wrote. “It was a lot of disorganization, political jockeying for power, and results, such as they have been, have taken forever to surface. I am appalled at what a mess AIDS research is in. In 35 years we should know more than we do.”

Mark Harrington, another activist who has lived with HIV for more than 20 years, was among a handful of ACT UP members who crashed the seventh ACTG meeting, in November 1989 in Bethesda. The meeting “was revelatory, but not in a good way. At the time, ACTG was floundering,” Harrington said.

Too much effort had gone into AZT, while “there were tons of trials that were ready to go but hadn’t been approved,” said Harrington, who helped plan and carry out ACT UP’s “Storm the NIH” demonstration in May 1990.

While the scientific community’s response to the activists was generally hostile and defensive, Fauci said he saw things differently. “I started to listen to what they said, and then I started to bring them into our deliberations about the design of clinical trials…. [T]hey became very valuable partners in our attempts to do something about HIV.”

Fauci spearheaded the creation of the ACTG’s Community Constituency Group (CCG), whose 24 members included activists, people with AIDS, people living with hemophilia, HIV-infected mothers and mothers of HIV-infected children, and former injection drug users. The CCG’s members are voting participants on the ACTG executive committee and core scientific committees.

Harrington, one of the original CCG members, served from 1990 to 1993 on the ACTG opportunistic infections and primary infection committees and has coauthored scientific papers. In addition to the CCG, every ACTG site is required to have an advisory board of community members.

Today, Harrington, who will be 55 years old in December but says his work, like that of the ACTG, is not done:

“I want to be here until the epidemic is really over… where we’ll have maybe not the definitive vaccine, but a vaccine that looks pretty good. I want to be sitting in this job, and when I look at the numbers, there’s not 50 000 new infections a year in the United States, there’s 125. It’s not 1.2 million worldwide, it’s like 20 000. That kind of thing.”

An Unmet Goal

The ACTG 019 trial represented “a major, major, major breakthrough,” but it was only the beginning, Fauci said.

 “[W]e also realized that with a single drug and an RNA virus it’s likely that sooner or later there would be the development of resistance, and that’s what we saw.”

He noted that one of ACTG’s major successes was the first early trials testing combinations of drugs aimed at keeping resistance at bay, which has led to highly active antiretroviral therapy, or HAART, used today.

Fauci looks back on the ACTG’s accomplishments with satisfaction. “What started off as a pure treatment network now involves prevention, vaccines, topical microbicides, pediatrics: it’s really well beyond the original core of the ACTG.”

On its website, the ACTG lists 20 ongoing studies (http://bit.ly/IMpHS7w). Some sites are working on eliminating the need for daily antiretroviral therapy. One approach is a long-acting antiretroviral given every 3 months or so, while another is a therapeutic vaccine that would boost the immune system so that the virus wouldn’t rebound once daily therapy was stopped. Plus there are new drugs to test as daily therapy, still important because of HIV’s ability to eventually outsmart drugs and develop resistance.

Fauci will be 75 years old in December but says his work, like that of the ACTG, is not done:

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