Trials by Fire

Community-based drug studies are full of good intentions. But are they based on good science?

February 1, 1996 By Scott Williams

Several HIV positive AIDS activists praise SPV-30 with glowing testimonials at an ACT UP/Golden Gate meeting in San Francisco's Castro district: "My quality of life has gone up drastically." "I feel so much better." "It lowered my viral load." This meeting is the latest pause on David Stokes' whistlestop tour promoting clinical trials of SPV-30, an extract of the boxwood tree and one of the hottest new therapies in the HIV treatment underground. By almost singlehandedly organizing a national community-based study of this previously obscure herbal extract from the forests of France, Stokes has become its lead defender, examiner and cheerleader.

With his crisp button-down shirt and WASPish good looks, Stokes defies stereotypes of the defiant, leather-clad AIDS activist. His transformation, in just a few months, into an outspoken national treatment advocate, however, fits the mold of the '90s revision of activist stereotype -- a person who carefully negotiates with scientific establishment figures and other activists to blaze a trail to better AIDS treatments.

"I used to be a person who told my doctor: 'Tell me what I have to take and let me forget I'm HIV positive,'" Stokes says. But when he went on disability, his attitude changed dramatically. "I wanted to better understand what I was taking and what my options were. The more I learned about toxicities of some HIV drugs, the more I was determined to find something more natural."

A great number of people with HIV can identify with Stokes' story. Sometimes we're undereducated about our treatment options and overeager to do something to curb the tide of HIV. We'll take the first prescription the doctor gives us. But often these drugs fail or cause side effects that are just as bad as failure.

Not surprisingly, then, the bitterness that rises with the approval of each toxic new drug has driven an increasing number of people to look outside the government and big-business trial networks for answers -- especially about nonpatentable natural treatments. The money and effort -- and even some answers -- are starting to add up. But while we're digging for answers, let's decide what to call our spade: Are these underground trials we conduct in the community actual legitimate clinical research -- or, ultimately, simply another form of treatment activism?

There's a big crowd of nauseated people with AIDS complaining of numb, tingling extremities -- and some of them are slowly withering away from even worse treatment toxicities. One would

think government AIDS researchers might more actively explore effective treatments that don't drive people to upchuck until they toss their pills out the kitchen window. Unfortunately, our government's scientists are influenced by a host of other agendas.

"The government lets the decisions on what drugs to test be determined by the peer-review process, or bringing together a bunch of respected scientists to set a research agenda," says Martin Delaney, founding director of Project Inform, one of the nation's premier treatment-information and advocacy groups. "They review the data on this drug and that drug and assign a priority to it. There is a certain inherent bias to this process, because the scientists involved share a set of beliefs that is probably naturally biased against so many of these [natural-derivative] drugs. Therefore, nothing of an unusual nature ever gets a high-enough score to warrant being tested with government funding."

This is depressing and probably old news for many people with HIV who have actively tried to influence the system. But the good news is that new diagnostic tests like PCR or branched DNA -- which show viral load within the body at a given time -- allow people to conduct trials in a way that was impossible a few years ago. Historically, trials have aimed to prove a drug's clinical or survival benefits, which are longer-term outcomes measured in months or years. With viral load tests, the effects of a given therapy can sometimes be measured in weeks (although it's not always clear what that data means). Exciting research is now being conducted by scientists and community members because of this technological development.

Dr. Anthony Fauci, director of the National Institute of Allergies and Infectious Diseases (NIAID), says a drug showing promise in an informal community trial may certainly advance to more formal, larger-scale testing. "However, you must show that the drug has some identifiable mechanism against HIV. You must show that the drug blocks HIV in some way in a test tube before it's tested in people," Fauci says. If this is achieved, a community-based researcher can submit results to the executive committee of the AIDS Clinical Trial Group (ACTG), the Community Program for Clinical Research on AIDS (CPCRA) or the NIAID AIDS Drug Selection Committee. Currently, these are the mechanisms the government has in place to allow new drugs to enter the drug-testing system at the government level.

With the advent of viral load measurements, community-based trials may be easier to conduct than they were in the old days, but it's still a difficult and time-consuming process. To understand the genesis of many of these issues, rewind to San Francisco in 1987. Project Inform was just two years out of the chute. One of the first community-based studies was their retrospective analysis of AIDS treatments people had been flying to Mexico to get. This in turn led Project Inform activists to launch testing of other anti-HIV drugs in a community-based setting.

"After some time attempting to run these clinical trials, we noticed that it didn't look like we were doing anything that wouldn't have happened otherwise [in clinical research]," says Martin Delaney. "Conducting legitimate trials was also very expensive and time-consuming. So we could only influence a minimum of research by this method. Through our advocacy work with NIAID and drug companies, however, we got a much bigger bang for our buck. We had bigger, wider

influence through advocacy than conducting research on our own."

A reputable grass-roots AIDS organization such as Project Inform abandoned their research in the community for solid reasons. So what does this historical example mean for research such as that fostered by David Stokes? "I think Stokes is really raising consciousness for the product and the need to study it," Delaney says. "I applaud him for approaching this the way he is. It is much better than many other folks who just try to sell their alternative treatment without any data. That's not fair to PWAs. However, if enough people become enthusiastic about SPV-30 through their experience [in Stokes' study], that will create the pressure to do a more structured study."

People wanting to investigate widely used but underresearched treatments need to be creative. One way is to collaborate with both the alternative and Western medical camps, says Donald Abrams, assistant director of AIDS services at San Francisco General Hospital. For instance, Abrams and colleagues at the Community Consortium in San Francisco are now working with Chiron (a biotech company) and using the bDNA viral load test to evaluate the effectiveness of alternative therapies used by people in the community. Efforts such as this are to be found in the vast field of government AIDS research, but very few formal programs have been launched to study treatments in broad community use.

One attempt is Real Treatments for Real People, a campaign proposing reform at the National Institutes of Health that's being spearheaded by various ACT UP chapters. Real Treatments acknowledges that little efficacy data exists for many therapies used regularly in the community, including herbs, megadose vitamins, antioxidants and anabolic steroids. Other issues important to the survival of PWAs, such as proper nutritional maintenance, are also largely neglected in government-sponsored AIDS research. The $60 million-a-year ACTG has no trials examining how nutrition can extend the lives of PWAs. With many people with AIDS now dying of wasting syndrome, this is an unfathomable research void.

"Real Treatments challenges the existing trial network structure and pushes a new agenda for research," says Kiyoshi Kuromiya, a Philadelphia PWA activist and editor/publisher of the Critical Path AIDS Project newsletter. "Trial networks are constantly being re-structured and shuffled about. These government researchers must realize that they can't just rearrange the deck chairs on the Titantic. There must be real reform."

Designing the type of community-based drug trials that can command the respect of top scientists is difficult, time-consuming and expensive. Also, organizers must make sure their trial does not duplicate an effort of government-sponsored trial networks such as the ACTG or CPCRA. Even though both organizations ostensibly have the same purpose -- to find treatments for AIDS -- their structures and methods of operation differ significantly. The ACTG is the government's granddaddy clinical trial and research network, based mainly at prestigious medical schools; the CPCRA is much smaller, with about one-quarter of the ACTG's $60 million budget. The CPCRA's mission differs in that it specifically attempts to include underserved populations in the clinical research process at the community level and focuses on easily measured studies that don't require a lot of specialized tests or equipment.

Some activists, such as Chicago's Michael Thurnherr, who sits on the national and local community advisory boards of the CPCRA, question the relevance of much of the ACTG's brand of research: "The ACTG is too expensive and inefficient. They have wasted so much money on large trials where much of the information ultimately is not used."

"Federal trial networks need to study drugs for which there isn't a profit motive [such as aspirin or vitamins]; otherwise research on those treatments is not going to happen," Kuromiya says. "The ACTG and the CPCRA are industry-driven rather than community-driven. People with HIV and AIDS have seats at the table [on advisory committees], but we can't overcome the fact that these government researchers are in bed with the drug companies. Between conference calls of our Community Constituency Group meetings, these researchers have had four or five meetings with the pharmaceutical company." That sounds like a good-enough rationale for David Stokes' trial.

After swimming through the great sea of potential alternative HIV treatments, a friend informed Stokes of an extract made from the boxwood tree that was showing promise in patients enrolled in a traditional double-blind, placebo-controlled clinical trial in France.

Stokes approached the company and pitched the idea of starting an open-label, relatively uncontrolled trial in the U.S. After much negotiation with the company and consultation with activists, a U.S. trial design was established: 500 people with HIV would get a six-month supply of the product in exchange for their blood-work results every two months. Enrollees could already be using any available treatment but were required to have been following that treatment regimen for at least two months prior to starting SPV-30. In essence, it became a large trial of combination therapies, with SPV-30 as the one constant in the equation.

The costs of conducting an investigation such as this can vary greatly, but Stokes estimates about $30,000 has been spent on operating and promotional expenses for the SPV-30 trial in America. The French pharmaceutical company Arkopharma has provided 500 people six months of the product, at a cost of about $150,000. Patients have provided trial investigators with their own diagnostic tests such as T-cell and viral load.

Preliminary results from the French trial of SPV-30 are due in January 1996. Anecdotal results from the American trial are promising thus far -- drops in viral load virtually across the board, with rises in CD8 counts and then in CD4s. Most patients report that energy and quality-of-life measures are up after some time on the treatment.

The early data on SPV-30 seem very promising at first glance, but the relatively open trial design -- with participants taking a range of other drugs -- is sure to raise some eyebrows in the scientific establishment (not to mention in ACT UP/San Francisco, which has aggressively denounced SPV-30 as a dangerous immune suppressor). According to Martin Delaney, one of the reasons many scientists discount uncontrolled trials is that their design makes it very difficult to isolate the specific effect of a drug. "There are so many variables out of your control, and so many ways in which people respond to drugs," Delaney says. "Plus, everyone's disease process varies. Unless you have a really potent remedy, matching a benefit to a treatment is very hard."

Locating the chemical ingredient that's active against HIV is "where a lot of these studies get thwarted," says Richard Klein, a public health specialist in the Office of AIDS at the Food and Drug Administration (FDA). "You must do chemical analyses that show you can get the active ingredient in dosage form. Large companies or the government often have this capability. Smaller-scale studies have problems with this sometimes."

Klein says the FDA looks for well-controlled trials with proper ethical review standards and consistent documentation of data. FDA staff, he claims, will help interested parties design drug trials that meet the specifications necessary for the agency's approval.

"There can certainly be well-designed community-based trials," Klein says, "even with a number of different therapies like in the SPV-30 trial. You may have a lot more 'noise' because there are more variables involved, but I believe you can still show an effect."

The difficulty of executing clinical trials shouldn't discourage people from seeking certain types of information. According to Anthony Fauci, trials seeking "broad-stroke answers" can be effectively executed in a community setting. "Community-based trials can tell us: Is it better to start a drug early vs. late? Is alternating a drug regimen better than staying on the same regimen? Is it better to prophylax or not for a particular opportunistic infection? Trials that are more difficult to conduct at the community level are those that require very intensive lab monitoring and a uniform, homogeneous patient population to show the results of a particular drug regimen."

Just being *perceived* as a legitimate player is important to many individuals conducting research in the community. In fact, when asked to go on record for this article about his company's community-based research on Cytolin, a new immune-based treatment currently under study, well-known HIV positive photographer Tom Bianchi declined a formal statement -- because he did not want the treatment associated with underground drug trials. Bianchi said that it was too dangerous for the future of his treatment to be perceived as underground or alternative. For that reason, he was dismayed over the title of an *Out* magazine feature about his trial, "Maverick Medicine." When the FDA's Richard Klein was asked to comment on Bianchi's reluctance, he said "it sounds like paranoia over potential capital investment" rather than worry over approval (or lack thereof) by government authorities.

Perception of legitimacy is but one example of the concerns facing community-based researchers. As daunting and pervasive as the scientific "establishment" mindset can be, it doesn't stop individuals who want and need answers. "As far as physicians are concerned, of course a controlled trial would be better," Stokes says. "But let's face it: If a large majority of patients are adding SPV-30 to their regimens and seeing an improvement, that's all I care about. For those of us in the community who want nontoxic alternatives, what should we do? If a lot of our friends are getting great results from something, what more do we need?"

Often, it seems that well-done community research mutates into a form that bridges the gap between community-based research and Big Brother trial networks. One example is the AIDS Research Alliance (ARA) in Los Angeles.

ARA helps administer a range of pharmaceutical and alternative trials. It collaborates with the government trial networks and drug companies, but also advocates an ethical and balanced approach to AIDS research unencumbered by government bureaucracy or pharmaceutical profiteering.

ARA serves as a central enrollment clinic for many AIDS trials in LA. Patients may come to its office and enroll on the spot in any trial for which they are eligible. ARA gives no primary medical care; instead, it focuses solely on clinical trials and advocacy. Its genesis is similar to that of Project Inform. Started in 1990 by Dr. Paul Rothman (who has since died of AIDS), the organization's original purpose was to look broadly at the field of potential HIV therapies in an effort to separate the wheat from the chaff. Over the years, however, ARA has evolved into a full-fledged player in clinical HIV research. The trade-off is that the organization, through its alliances with dozens of top AIDS scientists, may become a victim of the same politics that stifle big-budget trials.

Executive Director Gregory Britt feels ARA is insulated from a lot of the negative effects of "mainstreaming." He points out one of ARA's major advantages over government-sponsored trial centers -- the ability to adapt in the absence of government bureaucracy. With its resources coming primarily from private funding, ARA is able to move research along more quickly than many government-sponsored programs. "The critical factor in our still being around today is our ability to change and respond," he says. "The whole pipeline of drug development has radically changed." Also, ARA focuses on human clinical research, rather than studies that test the effectiveness of drugs in test tubes.

One of ARA's greatest clinical research victories is its role in the 1993 approval of clarithromycin for the treatment of *Mycobacterium avium* complex (MAC). "It's our hallmark success story testing drugs in the community," says Britt. The drug was being studied in Europe as a treatment for MAC, and ARA brought it to the United States for testing in private physicians' offices. Data from its trial was instrumental in the FDA's approval of the drug for MAC treatment.

Unlike most big trial networks, ARA has not focused exclusively on Western pharmaceuticals. Garlic has been used extensively in China for more than a thousand years to combat gastrointestinal infections. ARA launched a small trial of a garlic extract, Allicin, enrolling 16 PWAs with cryptosporidiosis. Fifteen patients showed a dramatic reduction in symptoms, and four have repeatedly tested negative for the crypto organism -- an eradication never before documented in people with both crypto and full-blown AIDS.

Britt demonstrates that a community-based group as large as ARA does not have to lose touch with the needs of the community it serves. "One of my big pushes is that we need to move away from drug-based research and toward patient-based research. This means we need to recognize that we're not trying to find the best drug, we're trying to cure patients," Britt says.

With the limitations of traditional anti-HIV drugs, Britt's statements sound like a clarion call. A magic bullet against HIV may be years away.

In the meantime, advocating for and executing these community-based drug trials isn't an easy

undertaking, but such activism can change more than the research landscape. As David Stokes says, “I never thought of myself as an activist before my involvement with SPV-30. Writing checks to AIDS organizations used to be my way to help stop the epidemic. How things change! It is so much more rewarding to help people find things that help them live longer lives.”

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