Start Making Sense

Stop placing short-term individual need over long-term benefit for all

August 1, 1995 By Peter Staley

I am your typical self-empowered person living with HIV. I'm a gay, white male with a personal physician who has a large AIDS practice. I subscribe to all the AIDS treatment newsletters. I know and frequently talk with other people living with HIV. I even have a support group. And with Project Inform's Martin Delaney comes to town to speak about the latest treatments, I'm there. I'm aggressive. I've bought drugs from the underground. And since AIDS clinical trials have heretofore failed to provide clear-cut answers to my treatment questions, I've made best-guesses, relying on anecdotal information and vague clinical data. And I"ve been lucky: I'm still alive and relatively well.

In this light, the notion that every citizen with HIV should have the right to access any new drug that shows some promise of efficacy (however meager or ambiguous) is certainly appealing. Given the cult of individuality that American culture has so efficiently enshrined, it seems almost patriotic to demand universal access to such untested drugs. But should new and perhaps more informative clinical trials be held hostage to this demand? Should long-term improvements to an inadequate clinical trial system be sacrificed for this short-term individualistic need?

Unfortunately, the AIDS self-empowerment movement seems to be moving away from the goal of prolonging life for as many people as possible. Instead, the self-empowered seek only to save themselves. The moral shift became clear this past summer, when preliminary results from a small phase II study of saquinavir, Hoffmann-La Roche's protease inhibitor, were released. The study—a 24-week, 302-patient, three-arm trial comparing a triple combination of AZT and saquinavir and AZT and ddC—showed the three-drug combo increased CD4 counts more than the two-drug regimens and that the suppressive effect of the triple combo on viral load was also better than the double combos. Given the short duration and small size of this trial, statistical differences between the arms in the disease progression or survival could not be detected.

Shortly after these results were released, the Treatment Action Group (TAG, which I cofounded) got word that Roche was planning to ask the Food and Drug Administration (FDA) if it could immediately file for accelerated approval of the triple-drug combo based on their experience with 99 patients. In a letter to the FDA Commissioner Dr. David Kessler, TAG wrote the following:

"We urge you not to invite Hoffmann-La Roche to apply for accelerated approval of saquinavir until

we can complete further discussion between FDA, its Advisory Committee, the company and people with AIDS/HIV." This was the first time any AIDS activist had said "not so fast" concerning a drug's approval.

Needless to say, the proverbial shit hit the fan. Adding fuel to this fire, TAG's letter went on to suggest a novel approach to further testing of saquinavir. Instead of a traditional expanded access program, we suggested that Roche initiate a large, simple trial (LST) comparing two doses of saquinavir to a placebo in all HIV positive patients with CD4 counts less than 500. Unlike traditional AIDS studies, there would be no restrictions on the use of other antiretrovirals. Very important, this study would be accompanied by a salvage protocol providing saquinavir to patients who have failed on all standard therapies or who have less than 50 CD4s. If the LST were further stratified using high and low CD4 ranges, we originally estimated a trial size of 18,000 patients.

Community reaction to our letter and suggestion was initially one of shock. How could we ask the FDA to delay a drug's approval and suggest instead a giant study using a placebo? The answer, simply put, is: If you accept the premise that our goal with antiretroviral research is to prolong life for as many people as possible, then our desire for early access to a promising treatment must be balanced with a desire for reliable information on the treatment's ability to prolong life.

Maybe you believe that you can prolong you life by custom-tailoring a treatment regimen with early-access drugs and your doctor's close monitoring. But where does that leave the majority of people with HIV who aren't self-empowered? What about those who aren't gay, white men with personal physicians? In the Medicaid clinics and hospital emergency rooms of New York City, Newark, New Jersey and Miami you'd be hard-pressed to find a person with AIDS on combination therapy. Standard therapy is AZT as long as you can tolerate it or until you die, whichever comes first. The early marketing of ddI, ddC and d4T as not translate into real access of anyone except the self-empowered. Without studies that confirm any clinical benefit from these drugs, most doctors won't bother with them unless pressed by a self-empowered patient.

And just because someone's gay, white male doesn't guarantee that they'll join the self-empowerment movement. For every self-empowered queen like myself who knows the difference between a protease inhibitor and a nucleoside analog, there are many more gay men who choose the easier path of denial until it's too late.

Perhaps the time has come to defer immediate hypothetical benefit—often couched in terms of right-ff-access—in favor of near-term and long-term benefits for all of us. This is known as altruism. By definition it means that individuals give up some immediate benefit for the longer-term benefit of the group.

It may be hard to frame this debate in terms of selfish individualism versus altruism or symptomatic versus asymptomatic, but demanding access for the individual without insuring a process to benefit the entire group becomes just that: A small circle of people in the know may benefit while the majority is left with nothing. We should strive to do better.

TAG first proposed to pinpoint the problems. We knew that our antiretroviral trials to date had failed to produce much in the way of useful clinical data. After a decade of research, we know only two things for certain: AZT can delay progression and extend lives in people with symptomatic disease, and ddI is better at delaying progression tonew AIDS-defining events than AZT in people who've taken the drug. So why don't we know more? Do the other drugs not help a all?

After the first trial comparing AZT to a placebo, where the treatment effect was very dramatic, AZT became the active control arm in all the future trials. But even while we switched from using a placebo control to an active control like AZT, we didn't generally increase the trial size. Statistically then, most of these subsequent trials were only large enough, or powered, to detect at least a 50 percent clinical superiority over AZT. We were looking for home runs. We were wishing and hoping for a penicillin for AIDS. And we still are. However, the antiretrovirals thus far haven't been home runs, though they may be singles or doubles. Unfortunately, we have so far missed the opportunity to detect any moderate benefits.

Some activists have said that detecting moderate benefits isn't worth spending the extra money on. What if a home run is not just around the corner? Unitl we find one, we could achieve major treatment effects incrementally: One moderte effect on top of four singles taken together gets you to home base. We have got to be prepared to make the best of the worst case scenario. Our arsenal over the next ten years may be limited to five nucleoside analogs and two or three protease inhibitors. If there are singles and doubles in there, we need to know it.

Hoffmann-La Roche tried to pull a fast one. This was the company that brought us ddC on accelerated approval and then failed to honor its post-marketing agreement to conduct adequately controlled phase IV studies to confirm any clinical benefit. Sorry folks, but we just don't know whether ddC works or now. This summer, they wanted to subvert the accelerated approval regulations even further. Saquinavir had been in clinical trials less than one year, only 99 patients had tried the proposed combo indication and there was no expanded access program providing real-world, long-term safety data.

In contrast, when Bristol-Myers Squibb went to the FDA seeking accelerated approval for d4T, there were five years of experience with the drug, an expanded access program with 10,000 patients and a medium-sized study in progress to assess its clinical benefit. In the end, Tag's letter to the FDA asking them to hold off on saquinavir wasn't necessary. The FDA informed us that they had already told Roche it was jumping the gun. TAG is not against accelerated approval. If the data is good and the confirmatory study is up and running, we will enthusiastically support the anticipated filing for saquinavir's approval approximately six months from now, well ahead of similar filing times for ddI, ddC and d4T.

As for TAG's proposal for a large, simple trial, the knee-jerk potshots that many initially threw our way are now subsiding and others are giving the LST a serious look. The most common criticism involved the use of a placebo: "It's unethical, and besides, nobody would enroll." A traditional placebo would indeed be unethical. You're given a dummy pill, and the trial prohibits you from taking any other antiretrovirals. This ensures the homogeneity necessary when studying small

numbers of patients.

But in a large, simple trial, everyone is free to take whatever antiretrovirals they would have been taking outside of the trial. By using this kind of placebo control, we avoid having to make all patients take AZT—for example, there may be patients who don't want to take AZT or who have already failed on AZT. The LST lets the patient choose what he or she will take in addition to study treatments. And finally, if the patient later qualifies for the salvage protocol, they could switch over and receive the protease inhibitor.

While there have been many other issues raised about TAG's call for an LST, the accusation that we're holding up access to promising therapies is ludicrous. In the end, LSTs might not be the way to go, but will the status quo in AIDS drug development provide us with the knowledge we need to save our lives? If not, can answers as well as access become our common goal? Let's find out.
