Put Up Your Nukes

In the match of the millennium, most docs put their money—and their patients—on early intervention against HIV. Yet “hit hard, but wait” may be the best bet.

May 1, 2000 By David Barr

It’s the mantra that many AIDS researchers, doctors and advocates have been chanting ever since the first antiretroviral drug came on the market 13 years ago: “early intervention,” or in popular lingo, “hit early, hit hard.” Both mean the use of antiretroviral drugs by people who have HIV but not yet AIDS—the asymptomatic and untreated who still make up the largest group of HIVers, many of whom won’t feel sick for years, whether they take a pill or not. But will starting therapy early help them live longer and better lives? Sadly, there’s not enough data to say, but a look back at the not-so-distant past may shed light on why there’s a controversy.

In 1989, the government developed the first guidelines for early intervention. The only drug available at the time was AZT. That drug was recommended for all HIVers with fewer than 500 CD4 cells. The recommendation was based on one never-completed study, in which the people on AZT saw their CD4s go up over a 48-week period, while those not on AZT had no CD4 increase.

By 1993, we knew that that recommendation was wrong. Although CD4 cells increased, the people who started AZT early did not live longer than those who started AZT later, at 200 or fewer CD4 cells. Later recommendations to treat HIV early—with AZT/ddI and AZT/3TC, for example—have also been wrong. Not because treating early is a bad idea—it is a great one if treatment cures the infection. But if treatment has only a limited benefit, then we need to carefully consider when is the best time in the course of a disease to intervene and use that benefit. Treatment carries its own risks, such as the development of side effects or drug-resistant virus that could respond poorly to future treatment. In an illness like HIV, which takes a long time to develop, the question of when to start treatment is particularly difficult to answer. Prior to the introduction of protease inhibitors and highly active antiretroviral therapy (HAART) in 1996, the drugs we had were not good enough to do the job.

Since then, something remarkable has happened—something none of us could have imagined in the dark days of 1993. Death rates from AIDS have plummeted nationwide, and while there are differences in the rates of decrease among different populations—a stunning indictment of the inequities in our health care system—no group has been exempt from the good luck. Clearly, HAART is effective. The question is: How do we use it most effectively over a long period of time?

The Department of Health and Human Services first issued guidelines on the use of HAART in 1997. (I'm a member of the guidelines panel.) Although the guidelines are meant only to provide a context for deciding whether or not to start treatment, they are usually interpreted as recommending HAART to every HIVer with fewer than 500 CD4 cells and/or a viral load of 20,000 copies or more. Even more important, the Food and Drug Administration (FDA) has licensed makers of approved antiretroviral drugs to promote treatment to all people with HIV.

The research on hitting hard—that is, using at least three potent, compatible antiretrovirals—is pretty solid. But what about hitting early? Research shows that hitting early will raise CD4-cell levels and lower viral load. But, as in 1989, we have no idea whatsoever if early use of HAART helps people live longer, healthier lives. The studies have not been done. The AIDS Clinical Trial Group (ACTG) and the Community Programs for Clinical Research on AIDS (CPCRA) are not doing them. Industry is not doing them. The FDA is not requiring them.

But there are some things that we do know. We know that people have a hard time adhering to their regimens and that poor adherence leads to drug resistance. We know that there are fewer treatment options for people whose virus has broken through their initial HAART regimens. We know that some side effects lessen our quality of life and others are life—threatening. So we have lots of data that hitting early can be harmful and no data that it is beneficial.

This realization alone should be a key factor in determining the next round of treatment studies. When to start therapy and when to switch drugs are still the questions. But even under the best circumstances, these studies won't bear fruit for at least five years. What about patients making treatment decisions today? They won't have the data they need—so maybe we should at least exercise caution. Is it time to alter the guidelines? Or at least take another look at them?

I am not anti-HAART. I take anti-retrovirals and am probably still alive today because of them. But I had AIDS when I started HAART. Would starting earlier have helped me or only subjected me to side effects and drug resistance, making later treatment ineffective? The miraculous decreases in deaths reflect the success of HAART in people with AIDS, not in the asymptomatic. How many people has HAART already failed? We don't know. What is HAART failure anyway? Usually it is defined as virologic failure—your viral load fails to get or stay undetectable—which means that HIV disease will start progressing again. But if HAART fails me today, I am not likely to get Pneumocystis pneumonia tomorrow. It will take some time for virologic failure to turn into illness and death. Therefore, if we are causing more harm than good through early use of HAART, we won't know until it's too late. By the time the death rate starts to climb, the damage will have been done.

AIDS activists have been phenomenally successful: HIV medications are approved faster than any other drugs, and protease inhibitors were approved faster than any drugs in history. But that success is a mixed blessing. Drugs get out of the pipeline faster, but with less data about how to use them properly. And once the drugs hit the market, it becomes harder to do the randomized, controlled studies necessary to find out how best to use them.

In addition to studying early intervention, we have to make sure that studies of late intervention are done. Most new drugs are studied in people who have never taken antiretrovirals. But salvage, or "third-line," therapy should be an essential part of AIDS research; it will become only more critical as HAART fails more patients. As new drugs are developed, we must make certain that industry is researching their use for people no longer benefiting from current therapies. The drugs we have now are not a cure for AIDS. Learning how to use them properly while pushing for new and better treatments is an essential part of our mission. There is so much work to do.

PROS AND CONS

Best Case

- Dramatically reduce viral load and thus prevent dangerous mutations
- Minimize damage to the immune system
- Delay progression to AIDS and improve longevity
- Reduce chance of short-term drug toxicity because body is healthier

Worst Case

- Reduce quality of life from drug toxicity and side effects
- Develop drug resistance earlier
- Knock out future anti-HIV options
- Increase risk of transmitting drug-resistant virus
- Develop long-term toxicity and dangerous side effects

DOWN FOR THE COUNT

Like many AIDS terms, early intervention isn't as simple as it sounds. For one thing, it can refer to two different situations requiring quite different responses. Most experts agree that initiating an aggressive treatment regimen within a few weeks of infection can deal the virus a blow hard enough to encourage a better long-term immune response. Some believe that such a regimen can even be stopped after six months or so.

Of course, this advice doesn't help most newly diagnosed HIVers, who either aren't sure when they got the bug or are more than a few weeks away from the big event. For them, as David Barr

explains in his essay, some experts are increasingly concluding that “hitting early and hitting hard” may be a less effective approach—and perhaps more harmful long-term—than starting after CD4 counts are seriously depressed. Current U.S. guidelines recommend therapy for those with fewer than 500 CD4 cells or viral load counts above 20,000, if the patient is ready. The more-conservative British guideline is to start when CD4s drop below 350. But now, more and more researchers say that for HIVers without symptoms, it may be even wiser to wait until CD4s fall below 200. All agree that more research is needed.

Results from two recent studies have helped sway many researchers and clinicians to the “wait and see” position. In one, Andrew Phillips, MD, of Britain’s Royal Free Hospital Medical School, analyzing four large studies in a report delivered last December, concluded, “Given the current evidence, there would appear to be no compelling case for starting therapy with a CD4 count above 200 unless the patient is particularly committed to starting therapy or is experiencing symptomatic illness.” Also last December, results were reported from a Swiss study that followed 3,000 HIVers for three and a half years. Researchers, who focused mostly on injection-drug users, concluded that “deferring HAART may not be detrimental.”

—Jeff Hoover
