Success Has Made a Failure of Us

A veteran looks at where treatment activism lost its way

May 1, 1999 By Mike Barr

In January a frantic fax from the Coalition for Salvage Therapy (CST) arrived at my desk headlined *"ABT-378 salvage therapy needed NOW!"* Having cut my teeth on ACT UP drug demos a decade ago, I found its desperate dramatics familiar enough: *People are dying, the current combos have failed them, new drugs will save them.* But there's one little hitch: It's not at all clear that 378—Abbott's new protease inhibitor, whose timetable for expanded access and FDA approval CST wants to speed up—is the eagerly anticipated messiah.

CST calls for Abbott to test the drug in patients in dire straits. This, though, is unrealistic; drug companies are ever loath—especially so early in drug development—to undertake an acid test that almost invariably yields dowdy data. With amprenavir, Glaxo's new protease inhibitor, performing dismally in heavily pretreated people, HIVers at the end of their hopes have understandably latched onto 378 as their salvation. To date, no trials of 378 as salvage therapy have been conducted. Even so, because it's reported to be 10 times as potent as its vile predecessor, Norvir, some are convinced it will slay virus that has developed even massive protease resistance. But even GMHC's Dave Gilden, a CST stalwart, reports that 378 "is hobbled by many of the same mutations that affect amprenavir." Still, the grandly self-anointed CST, which boasts some of the nation's top names in treatment advocacy (Project Inform's Ben Cheng, Dr. Howard Grossman, TAG's Spencer Cox and others), has made immediate access to 378 its new holy grail. What a waste.

Don't get me wrong. I hope that 378 turns out to be the wonder drug some expect it to be. But if the past holds any clue to the future, 378 is surely to disappoint. Whether it's available tomorrow or a year from tomorrow ultimately makes little difference. And I worry that our flagging energies are being needlessly diverted. Strung along and strung out, we have for a decade now fetishized nearly every new drug *du jour*—usually due to lack of adequate information and clinical experience. In fall 1995, everyone "failing" antiretroviral therapy *had* to have 3TC, thanks in large part to a marketing blitz by Glaxo's PR dynamo. What happened? 3TC flew off pharmacy shelves, and patients became resistant to it in a matter of weeks. A few months later, everyone *had* to have saquinavir. Desperate HIVers hoping that the first protease inhibitor out of the starting gate would save them soon developed resistance to it—and at least partial resistance to all the protease inhibitors that would follow on its heels. Recently we have pinned our hopes on, in rapid succession, abacavir (Ziagen), adefovir (Preveon) and efavirenz (Sustiva). Not only have their

benefits eluded patients who had burned through other combos, but more important, their piecemeal, promiscuous use led to the squandering of real opportunities for survival. Such quixotic self-delusion would be laughably absurd if its consequences weren't tragic. Why are activists repeating the follies of our history? Why have we grown so big only to think so small?

In her March *Esquire* cover story, "The Virus at the End of the World," *Newsday* AIDS reporter Laurie Garrett quotes Spencer Cox lamenting, "Worst case, it's 1987 all over again"—for an increasing number of people with HIV, there are no effective treatments. Guerrilla clinic retro-potions such as NAC, peptide-T and DNCB are likely to resurface, since none has yet been proved a complete dud. If, indeed, it is 1987 again, then it may be time to trot out the military fashions, the alarmist agitprop and some desperate but creative thinking. Instead of chasing mindlessly after yet another me-too nuke or second-generation protease like a drugged-out hamster on its wheel, why can't we focus instead on innovative approaches to anti-HIV therapy? Where we are currently following, we need to begin leading—once again. That there's admittedly little to go on is a function more of our own myopia and complacency than of a deficit of scientific leads. Even middling progress with genuinely novel approaches would surely beat the blind alley we're being led down—by the pharmaceutical industry and CST, hand in hand.

In March 1997, the editor of *Nature Medicine*, Adrian J. Ivinson, challenged the then-euphoric antiviral vogue, noting that the body's immune control of HIV is no better after extended viral suppression than before. He concluded that "these observations do not bode well for a long-term solution to keeping the virus at bay…. A less fleeting success is likely to involve a combined antiviral and immune-based approach." And since immune interventions act on the target cells for HIV—rather than elusive HIV itself—the emergence of drug resistance is less likely. The rise and fall of HAART has, ironically, brought us full circle to where we first started: Only the immune system can clean up this mess.

1. How to boost the body's own production of HIV fusion inhibitors?

For over two years, we've had ample proof that tiny soluble proteins called beta chemokines can block HIV from fusing with uninfected CD4 cells. Why are we not frantically hunting for agents to increase our natural output of these fusion inhibitors? A molecule that naturally binds to the CCR5 receptor, dubbed RANTES, has been shown to dramatically inhibit HIV. And HIV-infected individuals whose CD4 and CD8 cells produce higher than average levels of RANTES have significantly lower viral loads and almost no CD4 cell loss. The same is true for at least one of the natural binding proteins for the CXCR4 receptor, which many researchers consider a superior target. Tinkering blindly with these ubiquitous receptors, though, is not without its risks.

2. How to keep the killer CD8 cells killing?

In a recent report, "The Most Potent Antiretroviral Weapon: Cellular Immunity," University of Texas immunologist William O'Brien wrote that "CD8 cells have a viral load effect [against HIV], which makes the antiviral effect of HAART look sleepy by comparison." Cytotoxic T lymphocytes (CTLs) have long been known to boost the body's control of HIV during the asymptomatic period. Recent papers in Nature and Science bolster this observation. The trouble is, CTLs need "help" from CD4 T lymphocytes in order to function effectively. With CD4 cells dwindling in number and function as a

result of HIV infection, CTL's anti-HIV response is often not up to snuff. New research in mice with Immunex's so-called CD40 ligand suggests that this intermediary signaling link between CD4 "help" and CTL function may be a bull's-eye for immune enhancement. Also promising is the interleukin-2 (IL-2)-like cytokine, interleukin-12 (IL-12), from Genetics Institute, which encourages the division and repopulation of CD4 cells. Unlike interleukin-2, however, IL-12 also seems to encourage the CTL activity of CD8s. Some small studies of IL-12 for HIV are currently underway at the National Institutes of Health. Finally, therapeutic immunization with various vaccine products known to boost anti-HIV CTL activity (most notably, the avipox vaccines of Pasteur Mérieux Connaught and Apollon's and Merck's DNA vaccines) could result in improved immune control of HIV.

3. Whatever happened to the antiviral/immune suppression one-two punch?

First advocated by Joseph Sonnabend, MD, in the mid '80s and, more recently and publicly, by TAG's Mark Harrington and Gregg Gonsalves, deliberately dampening the immune system at first seems wildly counterintuitive in an illness characterized by immune deficiency. But HIV may be a disease less of immune suppression than of immune dysregulation: hyperactivated CD4 cells, aberrant cytokine production, chronic inflammation and overproduction of antibodies. The potential role for immunosuppression, then, would be to counteract the rabid overstimulation of a complex immune network ratcheted out of control by HIV. For years now, we have had data from Europe suggesting a CD4 cell increase and clinical benefit from the use of immunosuppressive prednisolone and cyclosporin-A in early disease. Is there a role for selective immune suppression in advanced illness? We may never know.

4. Where are all the novel compounds?

Lip service is often paid to the search for so-called new targets against which to direct new classes of drugs: HIV's "zinc finger," its integrase protein and its various structural genes now make up a familiar wish list at scientific symposia. Unfortunately, clinical research is pretty much stuck in the same rut as it was in 1987. Most antiretrovirals currently in use, we would do well to remember, were not designed specifically for use against HIV. Rather, they were pulled from dusty laboratory storage shelves after they failed (or outlived) the diseases for which they were developed. Quite frankly, we just got lucky. Once the nucleosides and the souped-up renin (né protease) inhibitors were found to work against HIV, everyone scrambled to copy them. The rest is history. So are the days of low-investment, serendipitous discovery.

The problem is the snail's-pace progress made in the identification and development of biologically relevant screens with which to discover new classes of drugs. We keep getting barely tweaked versions of the same old drugs partly because the screening systems used to ID them are well established, tried and true. Drug discovery programs cry out for activist attention but get precious little.

I wonder if Project Inform's Immune Restoration program is realizing its full potential. Nothing like it exists anywhere in the country, but all we have gained is IL-2. Is the program dying of neglect? TAG and amfAR cosponsored a revolutionary think-tank on viral reservoirs at MIT last winter. Note to CST: Similar success with a summit on cellular targets and immunotherapy is needed.

Earlier this year, reports of a handful of “Berlin patient” wannabes—recently infected individuals who stopped therapy and remain free of detectable virus—made headlines. Seeking to mimic these provocative results, chronically infected cutting-edge HIVers who have enjoyed “undetectable” status for two years or more are sending out tubes of their blood to have it checked for CD4 cell proliferation to key HIV core proteins. The tantalizing possibility is that positive evidence of such a CD4 response might be proof that their immune systems have learned how to control HIV—that they, too, could stop their meds without HIV lunging back.

But even if these intriguing reports are confirmed by further study, this strategy is out of reach for a growing number of PWAs worldwide who, even when attacked with “mega-HAART,” can never get their viral loads back down to manageable levels. There’s simply nothing left in the treatment armamentarium—or pipeline, for that matter. Our leaders in San Francisco, Seattle, Washington and New York need to acknowledge these thorny truths as they begin to strategize and prioritize to keep us—and themselves—alive.
