Protease Inhibited

The first of the new antiviral drugs revives difficult dilemmas about research versus access

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Michael Brigette was in trouble, and troubled. Having started AZT over four years ago, the New York City resident had proven severely intolerant to several of the first generation of drugs to fight HIV. After a nasty case of ddI-induced pancreatitis, horrible neuropathy from d4T and ddC, as well as two cases of *Pneumocystis carinii* pneumonia, Brigette -- at 34 CD4 cells -- had no more antiretroviral treatment options. On December 7, 1995, the day the Food and Drug Administration (FDA) approved marketing of the first protease inhibitor, his doctor wrote him a prescription for Invirase, the brand name of Hoffmann-La Roche's saquinavir. But Brigette has yet to hand it in to the pharmacy. "I'm still wary of this drug," he remarks. "Even with my low T-cell count, I don't know which protease inhibitor is the best and whether taking saquinavir may limit my options even further in the near future."

Steve Visscher, another New Yorker with AIDS, had experienced a similarly frightful downward slide. "I'd been on every antiviral under the sun," he sighs. None stopped his continual CD4 cell drop, although an AZT/3TC combo did bring down his viral load somewhat. But when he went on saquinavir last August -- in combination with the other two drugs -- through Roche's compassionate use program, he began hitting pay dirt. Within a few months, his viral load dropped to almost zero, his CD4 cells went up, his minor skin infections disappeared and his overall energy was better. "At first, I was a little scared that I had jumped in too soon," he says. "But after much soul-searching I decided that if I was going to stay one step ahead of this disease, I had no choice but to step off into the unknown."

Brigette and Visscher are both HIV information hounds who carefully consider their treatment decisions. While Visscher felt comfortable with his choice, Brigette's angst originated with the evidence, acknowledged by Roche, that saquinavir is so poorly absorbed by the body that it can lead within a few months to viral resistance -- mutations possibly making HIV no longer treatable by that drug. His concern was magnified by some researchers' fear that PWAs using this drug might become *cross-resistant* -- unable to benefit from another protease inhibitor.

Just what Brigette might lose out on was made clear two months later, when headlines blared that the two protease inhibitors in line for FDA approval this spring -- Merck & Co.'s indinavir and Abbott Laboratories' ritonavir -- provide much more dramatic antiviral effects than saquinavir, and ritonavir appears to actually extend survival (see Promising Prospects).

The stakes are high, for both PWA survival and corporate profits. The annual wholesale price of saquinavir is $5,800, and higher prices are predicted for the next two protease inhibitors. With HMOs, AIDS Drug Assistance Programs and Medicaid all limiting reimbursement for expensive care (see "Upping the Ante"), it becomes especially crucial that PWAs get the best bang for their buck.

So in deciding whether to join the 15,000 PWAs already on saquinavir, Brigette faces a common dilemma. That dilemma, in turn, stems directly from past answers to age-old questions haunting the AIDS community: What do we want from pharmaceutical companies -- speedy development of a promising drug, no matter what its risks, or extended research to find a safer version, which may postpone access to it? Does the FDA have a responsibility to prevent marketing of risky drugs, or if it does approve them, to warn the public? Can some of the research be left to post-marketing studies? The history of saquinavir provides a case study in these tough choices, and an inkling of what may lie ahead with other protease inhibitors.

Hoffmann-La Roche prides itself on being the first company to identify HIV's protease enzyme -- which prepares and releases the virus to infect new cells -- as a potential therapeutic target back in 1989. British laboratories constructed a compound with anti-HIV activity stronger than any existing drug. In 1992, Roche launched clinical trials of saquinavir in the United States.

"We've been negotiating with the FDA regarding the approval of the compound since the day we began our trials program," says Dr. Miklos Salgo, Roche's director of clinical virology. In 1994, a six-month clinical trial combining saquinavir with AZT, ddC or both found that the 200 PWAs on the new drug had moderate decreases in viral load and increases of 25 to 50 in CD4 count. Based on these data, the company prepared to file for accelerated approval, using the mechanism adopted two years earlier under pressure from AIDS activists to speed marketing of promising drugs for life-threatening illnesses. This procedure allows the FDA to license drugs based on minimal evidence of drug effectiveness derived from modest numbers of PWAs' blood markers; no actual proof of impact on disease progression or death is necessary.

But in August, 1994, the New York-based Treatment Action Group (TAG), whose leaders had championed that innovation, shocked the AIDS community by asking the company and the FDA to hold off. TAG sought Roche's agreement to an 18,000-person long-term trial to insure collection of in-depth data. As TAG founder Peter Staley wrote in *POZ* ("Start Making Sense," *POZ* No. 9), "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."

Community reaction was swift and angry. More than 50 organizations united to successfully advocate preservation of the hard-won accelerated approval process. Roche rejected the large trial idea, but waited until August, 1995 -- a year later -- to file its New Drug Application. "The FDA only required that we submit drug activity and safety data on 500 patients taking Invirase for six months; we gave them much more," Salgo says. At last November's hearing of the FDA's Antiviral Drugs Advisory Committee, panel members asked some questions about incomplete research, but by then enough studies suggested saquinavir's modest, short-term benefits that the entire

community, including TAG, was demanding immediate access. The committee recommended approval and three weeks later, the FDA agreed -- a record 90 days after the company applied.

At the time, Roche and Merck promised to quickly initiate joint trials to settle whether saquinavir might create cross-resistance against other protease inhibitors used afterwards. Will they follow through? Dr. Ellen Cooper, then the FDA medical officer who reviewed the approval application of AZT, warned in 1987, “Once a drug is approved for marketing, it is very difficult to withdraw it. The FDA, in representing the public, has no way of ensuring the needed studies are done. The company may agree to perform certain studies prior to approval, but there is no practical way of enforcing these commitments.”

From Roche’s earliest studies of saquinavir, it was clear that no more than four percent of the drug (zero on an empty stomach) is absorbed by the body. Further research found that the dosage being used (600 milligrams three times daily) resulted in mediocre antiviral activity lasting only about 16 weeks. More worrisome, low drug levels appeared to produce viral resistance. One study found that half of those using saquinavir in a drug combination developed resistance within a year. “Roche knew they were dealing with a suboptimal dose more than two years ago,” says Dawn Averitt-Doherty, executive director of the Women’s Information Service and Exchange (WISE), an Atlanta-based advocacy group for women with HIV. But the company moved forward with large clinical trials using that dosage.

In 1994, Dr. Thomas Merigan of Stanford University obtained Roche’s support for a 40-person study of double and triple dose saquinavir. At the urging of community activists, Roche extended the study from 14 to 24 weeks. In September 1995, Merigan released results showing that the higher doses substantially increased the drug’s antiviral punch and reduced resistance, while only slightly heightening the risk of gastrointestinal and liver problems.

But what Roche applied for and the FDA approved last December was the lower dose, and post-marketing studies using that dose continue. Last year, Roche began developing a new soft-gel formulation which it believes will increase absorption to 16 percent and likely be cheaper. At least a year of testing will be needed to obtain FDA approval.

Should Roche have shifted research dollars sooner into development of the soft-gel version or at least into large-scale studies of a higher dose?

“That’s difficult to answer,” says Martin Delaney, founder of Project Inform, the San Francisco HIV treatment clearinghouse, “because saquinavir at its current dosage will probably benefit some PWAs whose CD4s have crashed or viral loads have shot up, while many who aren’t ’in trouble’ will just wait until the Abbott and Merck drugs are approved.”

Linda Grinberg, a PWA and board member of the AIDS Research Alliance of Los Angeles, also finds this a tough call. “Once Roche knew the dose was too low, continuing trials at that dose was unethical. But if changing doses would have delayed FDA approval, the company should have sought approval of both versions.” Averitt-Doherty says, “Roche was more concerned about being the first in line than getting the most effective product to market.”

Joy Schmitt, Roche's director of corporate communications, responds, "That's not entirely incorrect. There was an urgency on Roche's part to get this drug to market for people who needed to benefit from it." Her view is backed by John James, editor of *AIDS Treatment News*. "Because the drug is complicated to manufacture, switching to a higher dose would have indeed delayed the clinical trials, and, thus, FDA approval. Plus the much higher price would have prevented many from affording the drug."

Roche was not the only manufacturer facing dosing dilemmas. Merck began testing indinavir (Crixivan) in February, 1993. After studies at gradually escalating doses, researchers hit on a dosage which, in 24-week studies, reduced some PWAs' viral loads by 99 percent.

Delaney says Merck, thinking they had "the cure," prematurely geared up for full-scale production. But continued studies found that viral loads soon began heading back up. "From the start they should have studied a wider range of doses," Delaney maintains. Instead, he argues, corporate officials and research planners spent nine to 12 precious months testing higher doses and sorting their options until finally launching full-scale production of the higher dosage in January 1995. After that, observes Averitt-Doherty, thriving on the drug since joining a trial 18 months ago after her CD4 cells nosedived, "Merck worked incredibly quickly, although still not fast enough for most of us."

By early 1995, Merck researchers found that indinavir as monotherapy generated cross-resistance to other protease inhibitors. But they really stirred up a hornet's nest by suggesting that saquinavir, when used first, might similarly cause cross-resistance. This sparked an all-out "he said-he said" war between spokesmen for the two corporate rivals.

Dr. Emilio Emini, director of antiviral research at Merck, says, "It is very possible that resistance to saquinavir could put you on the road to indinavir resistance. When starting with one drug and then switching to the other after resistance has already begun, the development of cross-resistance may be well underway." Roche's Salgo complains that Merck's theory has received much more attention than it deserves.

Who's right? Most experts at a drug resistance workshop two days before the FDA committee meeting agreed that both sides were guessing. "But we *do* know how to find out," James wrote in *AIDS Treatment News*. "There is widespread consensus that a small clinical trial, combined with proper laboratory studies, could within a few months answer the practical questions about using saquinavir. The issue now is whether these companies...can cooperate enough...to conduct the studies."

Yet in approving the drug, the FDA did not exercise its authority to require cross-resistance studies. Dr. Jeff Murray, the FDA official who reviewed the saquinavir application, says he was satisfied with Roche's promise to follow up. "In the meantime, Roche is required to mention the possibility of cross-resistance in the package insert [the tiny-print enclosure], but not in advertising, until data from clinical trials report otherwise."

The FDA allowed other research lapses to go unremedied. While a request for approval of

monotherapy was rejected for lack of evidence of benefit, Roche won official sanction for combination treatment with any of the five approved antiretrovirals. Yet Roche had only completed combination studies with two, AZT and ddC. FDA advisory committee member Bill Bahlman, an ACT UP/New York activist, decried the company's failure to do the other three combo studies. Instead, Roche compiled data from patients in its lottery program for distribution of the drug, never designed for research purposes. Salgo claims this was sufficient to rule out dangerous interactions but concedes that "combination results cannot be extrapolated from these data."

Another lapse was an all-too-common one among drug developers. According to Averitt-Doherty, "There were not enough women in the saquinavir studies to do any reliable analysis of whether there are gender differences in safety or effectiveness." (Early studies had very low numbers of women; later trials included 12 percent.) Despite evidence presented by women's advocates that biological differences can produce important variations, the FDA has yet to require drug manufacturers to include adequate numbers of women in their studies.

By everyone's account, from day one, decisions about saquinavir were made in the context of intense community demand for new treatments. Michael Onstott, a PWA and board member of the San Francisco-based Healing Alternatives Foundation who has met with Roche researchers, says, "Part of the problem is with the activist community itself. We tend to beat down the doors for any new antiviral and brush aside some of the side effects or potential lack of long-term efficacy with the idea that these will be overcome in the next generation." Project Inform, TAG and other groups tried without success to persuade Roche and NIH to raise the dose used in studies, but never called for a broad campaign of community pressure.

James Driscoll, spokesperson for the Direct Action for Treatment Access in San Francisco, says he and other activists feared slowing down access. "We were disturbed by the problems, but felt that low-dose was better than nothing. And until last fall, we didn't know that the other companies' drugs would turn out as powerful as they did." Steve Visscher, the PWA on saquinavir, agrees. "If saquinavir didn't come out when it did, and I had to wait for the other drugs, I could be dead waiting for it."

Once the research showed even limited benefit, all sides agreed that FDA approval was essential. Averitt-Doherty says, "Nobody I know with less than 100 T-cells will tell you to hold up a drug if there's any benefit and it's reasonably safe. Access always comes first." ACT UP's Bahlman concurs. "The data was incredibly significant. Despite the questions of poor drug absorption and resistance, the FDA was faced with a combination of drugs (saquinavir/AZT/ddC) that produced results never seen before. We couldn't wait until every 'i' was dotted and every 't' was crossed -- people with AIDS wanted to take chances."

But treatment educators argue that the FDA failed to alert doctors and patients about the risks and how to minimize them. "There should have been an awfully strong headlined caveat about the low absorption and the risk of cross-resistance, so everyone had truly informed consent," says Kiyoshi Kuromiya, the PWA who directs the Critical Path AIDS Project in Philadelphia. Adds Project Inform's Delaney, "The FDA should have required the labeling to include both the high-dose study

results and a caution that the only proper way to use this drug is in a three-drug combination." Averitt-Doherty reflects on her experience giving treatment workshops. “Most PWAs, particularly in poor communities, don’t get their AIDS information from treatment newsletters and public forums -- they do what their doctor says. And most doctors look to the FDA for drug information.”

But more information about saquinavir’s risks and benefits may be a long time in coming. Joint cross-resistance studies promised by Roche and Merck have yet to begin. And Roche says that combination studies with two or more protease inhibitors, which many observers believe offer the best hope of effective therapy, must await the new formulation.

The caution offered by former FDA official Cooper still holds true today. While the FDA now has the right to withdraw a drug for failure to perform appropriate follow-up studies, such a decision would provoke huge political resistance. Spencer Cox, TAG’s antiviral director, explains that “pulling a drug after approval would require proactive evidence that the drug is ineffective or severely toxic.” Onstott of Healing Alternatives draws a lesson. "In the future, when we activists see faulty research, instead of deferring to the company, let’s advocate more fine-tuning *before* FDA approval."

Meanwhile, PWAs in urgent need of options must make decisions in a partial information vacuum. Michael Brigette, the PWA undecided about what to take, says, “I just need to be sure that the protease inhibitor I choose is the best one for me. I can’t afford to make any hasty decisions. What’s really strange, though, is that we know even less about the potential drawbacks of these drugs than we do about the possible benefits.”

But Steve Visscher, the one thriving on saquinavir, is philosophical. “In 1988, my friends marched on the FDA demanding faster access to AIDS drugs. We got it. With the good you’ve got to take the bad. Whether ’informed consent’ is as informed as we’d like, we’re getting access to drugs that a decade ago would never have been released this quickly. Could one of them turn out to cause horrible side effects later on? Yes, but I’m willing to take that chance. Now is not the time to slow down the process.”

With so much at stake, the dilemmas of access vs. information and risk vs. benefit continue to haunt those facing treatment choices. For the future, the challenge that faces the AIDS community as a whole is finding the right balance.
