



Ten Texts on Saquinavir

Its Rapid Rise & Fall

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INTRODUCTION

by Mark Harrington

16 June 2001

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If you don't have the survival data, how are you exercising your clinical judgement?... I find it hard to understand how anyone could feel that it is not important to know... Of course [the doctor] needs to know that. This is life or death. Why isn't that important?

– **Robert Temple, MD, FDA
Lasagna Committee¹, February 1, 1989**

If you are going to have accelerated review it is important to expose the [FDA advisory] committee to the Phase Three protocols before they are actually executed. The educational process and the consensus process that they represent are not trivial.

– **Thomas C. Merigan, MD
Lasagna Committee, February 1, 1989**

We are not against all drug regulation of any sort. We don't want ourselves or our friends to die from taking unsafe drugs and we disagree with the radical deregulators of the right who would abolish all efficacy requirements, and risk flooding the market with safe, but ineffective, AIDS drugs...

– **Jim Eigo, ACT UP/New York
Lasagna Committee, May 2, 1989²**

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¹ The Lasagna Committee, a.k.a. the National Committee to Review Current Procedures for Approval of New Drugs for Cancer & AIDS, was convened in early 1989 at the behest of then-President Bush and was chaired by Dr. Louis Lasagna of Tufts University. Its meetings were the scene of many interventions by the Treatment + Data Committee (T+D) of ACT UP/New York.

² Jim Eigo, Iris Long and Mark Harrington, *AIDS Drugs Now: Interim Report to the National Committee to Review Current Procedures for New Drugs for Cancer and AIDS*, Treatment + Data Committee, ACT UP/New York, May 2, 1989.

This is a story of desperation, expediency, compromise, and misfortune – the desperation of AIDS activists in the early and mid-1990s fighting with the government, with the drug companies, and with each other over how best to move new drugs forward through the testing and approval process to save the lives of those sick with AIDS and to figure out how to extend the health of those with HIV; the expediency of drug companies trying to bring forth new anti-HIV drugs as quickly (and often, as cheaply) as possible; compromises imposed by the government agencies that were most involved, the Food & Drug Administration (FDA) and the National Institutes of Health (NIH), and by the academic scientists who worked with NIH funds and played by FDA rules; and the misfortune of thousands of people with AIDS and HIV who suffered because of inadequate drugs, inadequate studies, and inadequate information – and, ultimately, because the drug in question, Roche's saquinavir, turned out to be a big disappointment.

It seems like a good time to tell this story again because there is so little institutional memory in the AIDS treatment activist movement, and the story of the last fifteen years is hardly the unblemished forward march of scientific progress it is sometimes portrayed as. The story raises issues which are always timely, illustrating unavoidable tensions between speed and care, thinking and feeling, common ends and contested means.

In mid-1992 I was the second community representative on what was then known as the AIDS Clinical Trials Group (ACTG) Primary Infection Committee (now dubbed the HIV Research Agenda Committee, or RAC). The committee, then as now, was the bastion of scientists who only grudgingly met the incursion of the activists into the ACTG starting in 1989, and were not used to dealing with us as equals. At one meeting, something bizarre took place. We were discussing the proposed study of an exciting new drug – the first protease inhibitor to enter clinical trials – called Ro 31-8959 and later to be known as saquinavir. There were some anomalies in the proposed study. Roche, which had done the phase I study, had not tested the drug up to the maximum tolerated dose (MTD). Most of the drug did not, it appeared, get into the bloodstream. This was of concern because it might weaken the drug's effect, or even lead to drug resistance. Moreover, the statisticians' report on the proposal stated that the study as designed would be unable to detect a moderate effect, if in fact the drug had one. Now we were sitting around the table discussing the proposal, and I kept bringing up uncomfortable questions about the dose and the design. There was an embarrassed silence and some shuffling of papers. Eventually Dr. Thomas Merigan – then the committee chair – and Dr. Ann Collier, who was to be the study principal investigator (PI) – left the room with the Roche representative and huddled in the hallway looking over some papers which displayed the preliminary dosing and potency information. Then they came back into the room and told us that everything was OK, the dose proposed for ACTG 229 looked just fine.

While I have the utmost respect for Drs. Merigan and Collier, this was simply no way to go about deciding to invest taxpayer dollars and commit hundreds of people with AIDS in a publicly-funded study. But Roche insisted and the ACTG was as desperately eager then as now to get its hand on the hot new drug du jour (or d'année, as the case may be). The letter I wrote to Dr. Collier expressing my concerns was politely brushed off. ACTG 229 duly moved forward and the ACTG randomized 302 AZT-experienced individuals to receive AZT plus ddC, AZT plus saquinavir, or all three drugs together.

Some of us were worried. Back in April 1992 we had gone through the grueling FDA Antiviral Drugs Advisory Committee hearings on Roche's HIVID brand zalcitabine (ddC). I had the misfortune to be the community representative on that occasion. My journal entry for the day, April 20, notes, From 4-7 [p.m.] the lame Roche presentation of their ddC NDA.

Everyone is appalled at their pathetic evidence of safety and efficacy. While I'd seen nothing whatever to convince me that the drug had any useful activity in the body, it was widely used on an extensive underground in the community (as Roche had refused to

establish an expanded access program), and was being touted by many prominent researchers as perhaps the most potent drug to use in combination with AZT. The night before the hearing we held a large meeting of community activists in a hotel room and debated the issue for a long time. Eventually I decided that, as my role was to represent the community, I would vote in favor of approval for ddC even though I saw no evidence that it was safe and effective. My misgivings were strong but in those days there was so little to offer people with AIDS that it seemed better to go along with majority sentiment. (I assuaged my conscience by voting “no” on the monotherapy indication and “yes” on the combination therapy one.)

Over the following two years the misgivings which I felt at that hotel room in Bethesda, and which were shared by many of my colleagues at AIDS Action Council, AIDS Action Baltimore, Community Research Initiative on AIDS, Gay Men’s Health Crisis, the People with AIDS Health Group, and others, grew into a feeling that the AIDS community, in its understandable desperation, was being manipulated by industry to demand the expeditious approval of inadequately tested drugs. The deal was that industry would provide the proof of safety and efficacy *after* approval. But with ddC, Roche failed to generate that evidence.

In early 1994 my ex-lover, Jay Funk, died of a virulent pulmonary Kaposi’s sarcoma after living with AIDS for more than four years. My own immune system was still fine, but I no longer felt like going along with majority sentiment in my activism. My colleagues in TAG felt the same way. Rather than being expedient or going along with mainstream sentiment it seemed better to think through what we really thought would be best for AIDS research, and for people with HIV, and put that forward as policy – to try and change the way protease inhibitors were developed, to get more information faster with bigger studies that would provide more access and better answers.

All year we had passionate discussions and debates about ddC, d4T, and saquinavir and the new protease inhibitors. How could we avoid, or at least learn from, the mistakes which had been made in studying the nucleoside analogues? How could the new programs of expanded access and accelerated approval, for which we had fought so passionately, fulfill their promise rather than degenerating into tools by which industry could manipulate us – We give you Parallel Track, you give us Accelerated Approval?

Eventually in mid-1994 we decided to go public with our concerns. The story that you are about to read describes some of the main events of that struggle. After the dust had settled, the field moved rapidly and unexpectedly forward into the era of highly active antiretroviral therapy (HAART), although whether or not saquinavir-containing regimens ever really were “highly active” remained somewhat controversial. Thanks in part to our intervention, saquinavir was not approved in mid-1994. By the time it was released, in fall 1995, two other much more potent protease inhibitors were not far behind. This was fortuitous, for had saquinavir been on the market a year earlier, thousands of people would have taken it, failed to suppress their virus, developed resistance to the drug, become cross-resistant, and not been able to benefit from the much stronger ritonavir or indinavir which came onto the market in early 1996.

Even though saquinavir benefited from being the first protease inhibitor on the market, it never was a big seller. When the U.S. HIV treatment guidelines panel put out its first post-HAART antiretroviral treatment guidelines in spring 1997, Roche’s Invirase was not among the drugs in the *preferred* category for first-line therapy. The company instigated a massive letter writing campaign to the panel, which had no effect.

In late 1997 Roche finally introduced the much more potent soft gel capsule formulation, Fortovase. But it had a high pill count and never really caught up.

Later in the 1990s Roche began to move on. Practically no one was using ddC anymore. Sales were too low to figure in the company’s annual reports. Invirase was receding into

the past. In its first quarter 1999 report Roche touted recent regulatory approvals received for Fortovase in the US, the EU, Australia, Canada, Switzerland and elsewhere, and claimed that “market reception has been very good”, noting that worldwide Invirase/Fortovase sales that year amounted to some 350 million Swiss francs (SFr), or about \$197 million. Luckily the company had licensed Viracept brand nelfinavir from Agouron for sale in many countries; Roche’s worldwide 1999 Viracept sales amounted to 430 million SFr or about \$242 million. As late as the first quarter of 2000, Roche reported that “sales of Viracept . . . continued to show double-digit growth.” But by the first quarter of 2001 the company reported “sales of the anti-HIV medicines Viracept and Fortovase were down for the quarter as a result of increasing competitive pressure.”

Regardless of the future of ddC or saquinavir, Roche will remain a presence in HIV research and care as 1) it is co-developing the fusion inhibitors T-20 and T-1249 with Trimeris; 2) its anti-CMV drug valganciclovir (Valcyte) received FDA approval; 3) its RT-PCR test kits are the standard of care for viral load testing; and 4) its pegylated anti-hepatitis C virus (HCV) interferon alpha Pegasys is poised to become the standard of care (when used with ribavirin) for HCV in both HIV-positive and negative individuals, at least for the near future. To its credit, Roche also appears to have learned to be more open and constructive with the community than was once the case.

Are there any lessons from the saquinavir saga? Perhaps there are.

- It would have been better if Roche had discovered the maximum tolerated dose (MTD) of saquinavir before rather than after moving into phase II. While this would have required a larger investment upfront, it would have had the effect of letting them market Fortovase rather than Invirase in late 1995, and they could have become a market leader.
- Moreover, it would have been better if Roche had studied the effect of suboptimal dosage on viral drug resistance earlier. Again this would have resulted in a higher dose moving into phases II-III.
- Similarly, it would have been better if Roche had designed larger phase III studies earlier. They ended up doing so anyway, and the studies showed what at the time was regarded as acceptable activity.
- Roche also didn’t bother opening expanded access programs with either ddC or saquinavir until just weeks before approval. This highly cynical maneuver helped build demand for licensure while holding people with advanced AIDS hostage to its commercial needs.

Other lessons apply to academic scientists, regulators, and activists.

- It would have been better for all concerned if the Primary Infection Committee had insisted on transparency rather than secrecy in deciding why it was moving forward with a suboptimal dose in 1992.
- At the same time researchers and regulators were complicit in allowing Roche to impose a shoddy dose and a shoddy design on the ACTG, and many activists went along with it at the time, fearing that otherwise “companies would leave the field.”
- We must not allow the implicit or explicit threat that a drug company will take its resources and go elsewhere to allow us to condone poor study design or the infliction of suboptimal drugs onto the market.

I am sympathetic to the dilemma of Dr. Kessler in 1992-1994, caught as he was between the not always consistent demands of AIDS activists, the opportunism of industry, and the need to provide incentives for drug companies to stay in AIDS research so that there would be better new drugs.

- In the post-HAART era it is time for the FDA to firmly insist that promised post-marketing studies and monitoring of long-term effectiveness and safety actually take place.

Finally, there are several lessons for activists. We in TAG made a mistake by not consulting more widely in the community before writing our incendiary letter to Dr. Kessler in July 1994. Had we shared our viewpoint more widely and earlier with other activists they may have been more understanding of the fact that we were not trying to stop accelerated approval, deny access, or delay the development of protease inhibitors as a class. Rather, we were trying to make accelerated approval fulfill its promise, utilize the pivotal efficacy trials themselves to provide access (and answers) and ensure that protease inhibitors were developed faster and more intelligently than the nucleoside analogues.

One more lesson for activists. I do not recall that anyone in TAG or amongst our allies publicly attacked or impugned the motives of any of those in the community who disagreed with our positions. The opposite was not the case. Too often many in the community have listened to divisive rumors from drug companies or have resorted to personal attacks rather than engaging other activists in serious discussion and debate. My hope is that by revisiting the long and dispiriting saga of saquinavir, treatment activists today and tomorrow can reflect on what has happened and apply the lessons to the changing and very different situation in the post-HAART era as HIV treatment moves into global settings where it has never been used before, and where the research issues in contention will be debated with as much passion and urgency as ever.

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ACCESS VERSUS ANSWERS*by Mark Harrington***(1996 version)**

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After Berlin, no one could credibly believe that AIDS drug development was on track. Indeed, it looked likely that the various initiatives AIDS activists had worked with FDA, NIH and industry to develop were actually impeding the gathering of useful information about safety and efficacy. The first generation of anti-HIV drugs, the nucleoside analogues – AZT, ddI, ddC, d4T and 3TC – just weren't very good, but the studies to prove their efficacy were designed over-optimistically. As a result, many studies were too small to show anything useful. The Concorde study questioned the use of early AZT and the use of surrogate markers like short-term CD4+ T cell changes to indicate longer-term clinical benefit. ACTG 155 questioned the prevailing, but never proved, dogma that two anti-HIV drugs might be better than one. It was time to take a critical look at the way drug trials were carried out, and to demand changes to resolve the issues raised by the nucleoside analogue trials.

ddI had finally been approved in 1991, after short-term surrogate marker data showed that, in AZT-experienced patients, those assigned to AZT continued to have a CD4+ T cell drop, while, at eight weeks, those switched to ddI had a CD4+ T cell rise of about fifteen per cubic milliliter of blood. This wasn't a very impressive T cell rise, but it was enough for FDA to approve the drug. One year later, data from the same study, ACTG 116B/117, confirmed that switching to ddI was, in fact, better than staying on AZT. The benefit was only modest, however, and the side effects of ddI included infrequent peripheral neuropathy and rare but fatal pancreatitis. At least we knew in 1992, however, with the clinical benefit data, that the giant experiment we started in 1989, putting 16,000 people with AIDS on open-label ddI through Parallel Track, must have benefitted at least some of them. Of course, an easier way to have learned the same information would be to have done a much larger 116B/117 trial, which would have obviated the need for a Parallel Track, and gotten the answer within six months, rather than three years.

Also in 1992, prodded perhaps by the continuing deregulatory interests of President Bush, FDA Commissioner David Kessler promulgated new regulations formalizing the process by which ddI could be approved. The Accelerated Approval regulations provided that a drug could be approved based on surrogate marker data (such as CD4 changes) if the marker was reasonably likely to predict clinical benefit.³ Drug manufacturers would have to promise to conduct post-marketing studies to prove their drugs actually provided clinical benefit. The promise of accelerated approval was clear – drugs which were safe and might be effective could be released sooner – but its downsides weren't as apparent. Long-term side effects may not have yet been observed at the time of approval. With its drug on the market, the sponsor had much less incentive to carry out promised post-marketing studies, and it would be impossible for FDA to remove an approved drug unless it caused truly ghoulish side effects. Ultimately, then, Accelerated Approval, if the company didn't keep its end of the bargain, threatened to replace clear answers about how to use new drugs with rapid access in a vacuum of relevant information for doctors and patients.

³ FDA, "Accelerated Approval of New Drugs for Serious or Life-Threatening Diseases," *Federal Register* 57:239, 12.11.92.

The result, for people with HIV and their doctors, was a confusing and contradictory situation. People were being told that these new drugs were vital and life-saving, but there was no data that they, in fact, saved lives, and they were expensive, inconvenient and toxic.

The first drug released officially under accelerated approval was Hoffmann-LaRoche's ddC, a popular drug at the time because small surrogate marker studies suggested that ddC taken with AZT might be superior to AZT alone. Activists had waged a frustrating and unsuccessful campaign to force Roche to release ddC on Parallel Track, dating back to G'dali Braverman's zap in San Francisco in 1990. Roche refused, and as a result, a flourishing underground grew up and thousands of PWAs went on underground ddC. To stoke up demand just before its FDA hearing, Roche sent samples of the underground drug to the FDA, which determined that the amount of ddC per pill ranged from none to ten times the recommended dose, which could lead to permanent peripheral neuropathy. Just before its scheduled FDA hearing, Roche managed to shut down the underground and cynically announced a sudden conversion to the idea of Parallel Track. They were equally cynical at the hearing itself. There was no data that ddC helped anyone. The only solid clinical study was one which showed that twice as many patients assigned ddC alone died in the first year than the number of deaths in the AZT arm. Its effects on CD4 cells were, if anything, weaker than even ddl's. The application made it through the committee based on a ridiculous six-arm study run by Margaret Fischl and Doug Richman comparing various doses of AZT and ddC in combination. There was the suggestion, but hardly proof, that perhaps some combination regimen might be superior to AZT alone. On the basis of this flimsy evidence, generated from a trial designed like a Hindu icon with many arms, all tiny, ddC was approved for combination use with AZT, and Roche promised a raft of post-marketing studies. Roche never carried out its commitment to undertake the follow-up studies and, in 1993, ACTG 155 dashed the hopes of those who believed that AZT/ddC was better than AZT alone in AZT-experienced patients.

If the ddl experience hinted that accelerated approval might work, the ddC one showed that, in the hands of an unscrupulous or opportunistic drug company, its requirements for post-marketing studies could easily be flouted. ddC really was a rotten drug, and Roche seemed like a rotten company.

A small group of activists, most but not all from the east coast – among them Gregg and I, David Barr and Derek Link, Lynda Dee and others – were increasingly upset at the cynicism with which industry manipulated Accelerated Approval, with the FDA's flaccid response, and with the access-obsession of other community activists, who no longer seemed to think drugs were worth studying once they were on the market, and yet who clamored endlessly for access to drugs in the early stages of testing. They seemed to believe that drugs were a cure in the test-tube, life-saving in phase I, health-prolonging in phase II and then, once licensed after Accelerated Approval, no longer worth studying and perhaps not even worth taking.

We felt, on the other hand, that activists were no longer representing people with AIDS and HIV if they did not insist that drug companies generate information informing how to use the drugs released under accelerated approval. Most people with HIV are not the polypharmacy maniacs who tended to show up at drug company meetings and FDA hearings. Many treatment activists represent a vocal segment of the community which is intoxicated with access, and has abundant access to health care and the latest information and experimental treatments. Most people with HIV, however, lack such access, and many do not want to take drugs which are toxic, expensive, inconvenient, and for which no clear evidence of benefit exists. From a public health standpoint, we felt we had a responsibility to confront the drug industry, the FDA and the community activists with whom we disagreed, to force them to design studies which would prove whether a given new drug was worth taking or not.

After Concorde and ACTG 155, we no longer knew – though, in the face of the evidence, many scientists and activists still maintained – whether early intervention was useful, whether short-term CD4 changes predicted longer-term clinical benefit, or whether combined nucleoside therapy was better than monotherapy.

TAG and our allies set out to fulfill the promise of Accelerated Approval and to rescue it from expedient distortion by drug companies. In December 1993, as I was finally leaving the ACTG and its Community Constituency Group, after a frustrating year of working with Fischl, Merigan et al. on the Primary Infection Committee, I wrote a valedictory report, *The Crisis in Clinical AIDS Research*, lambasting the ACTG and industry for trials which were too small, too short, naively over-optimistic, and which failed to generate clear answers about new anti-HIV drugs.

In May 1994, Gregg Gonsalves was asked to sit on the FDA panel reviewing data on Bristol-Myers' new drug d4T. The company, unlike Roche, had done a great job on its Parallel Track, enrolling 27,000 patients and comparing two doses of d4T (the lower dose proved safer) but, like Roche, its trials were unimpressive. Gregg predicted that its ongoing confirmatory study was too small to prove whether d4T was superior to AZT and the data, 18 months later, proved him right. Gregg could not in good conscience vote for accelerated approval for d4T, taking a step which drew TAG into a radically revisionist campaign to reform clinical research.

At this point, FDA approval hearings resembled scenes from *Alice in Wonderland*. Baffled by the d4T data, Advisory Committee chair Debbie Cotton asked David Feigal, Cooper's successor at the FDA's Antiviral Drug Division, "Is evidence required?"

"No," replied Feigal. In essence, for anti-HIV drugs, the Kefauver amendments were in abeyance.

"Is evidence allowed?" riposted Cotton.

"Yes," replied Feigal.⁴

Gregg, Spencer and Derek Link were livid when they returned from the hearing. Yet another drug would be on the market, and no one would know how to use it. On behalf of Derek Link, GMHC wrote a letter to the FDA recommending against approval. The same week, d4T was released.

That summer, several of the new protease inhibitors were in phase I trials in the U.S. and Europe. Protease inhibitors attack a different HIV protein than the nucleoside analogues, and potentially they could shut off viral replication in two different ways. They are complex molecules, much bigger than the nucleosides, designed by computer-assisted structural biologists, and they are expensive to manufacture.

In May, Roche announced the conclusion of ACTG 229, a study comparing AZT plus ddC plus its new protease inhibitor, Saquinavir, versus AZT plus ddC or AZT plus Saquinavir. The study showed modest increases in CD4 counts and modest decreases in HIV levels;

⁴ In Spencer Cox and Derek Link's remarks in *Rescuing Accelerated Approval: Moving Beyond the Status Quo*, a Report to the FDA Antiviral Drugs Advisory Committee by Spencer Cox, Dennis Davidson, Gregg Gonsalves, Mark Harrington, Carlton Hogan & Rebecca Pringle Smith, 12 September 1994.

benefits were greatest in the three-drug regimen. Saquinavir looked to be about equivalent to ddC, which didn't seem like much of a breakthrough.

Although fewer than 300 patients been on Saquinavir for less than six months, Roche prepared to file an Accelerated Approval request from the FDA.

TAG decided to undertake a campaign to ensure that a much broader discussion take place between activists, researchers, FDA, NIH and drug companies to develop a comprehensive approach to studying the protease inhibitors. We did not want to end up in five years with five new drugs on the market and no clue how, whether, or when to use them.

On June 16, 1994, in a letter which rocked the AIDS research establishment and sparked a nationwide controversy, TAG, GMHC, the AIDS Action Council and AIDS Action Baltimore wrote a letter to FDA Commissioner Kessler objecting to Roche's premature request for accelerated approval for Saquinavir, saying, "We feel that such an approval would penalize people with AIDS/HIV by setting an inappropriately low standard of evidential requirements that would govern the regulation of [all protease inhibitors]. We urge you not to invite Hoffmann-LaRoche 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." (See below, page 13). Unlike any previous Accelerated Approval, Roche had conducted not even a pretense of a Parallel Track, and there was no long-term safety evidence on Saquinavir in thousands of people, as there had been with ddI, ddC and d4T. We demanded that Roche implement a Parallel Track to gather safety (and possibly dosing) information before approval.

At a heated meeting between TAG, GMHC and FDA officials, including Kessler, we charged that the FDA was allowing industry to flout the requirements of Accelerated Approval and that if they approved Saquinavir now, no other protease inhibitor sponsor would ever bother doing a study showing whether their drugs worked or not. Certainly Roche's own record with ddC demonstrated that it was unlikely to meet such commitments. We demanded that the FDA sponsor a meeting to discuss how to design studies for the protease inhibitors as an entire class, rather than reacting to Saquinavir in isolation.

Antiquated activist dogmas had crashed in the face of the new situation, which we had helped to create. Nonetheless, the putative unity of the community, industry, FDA and researchers in their common belief in surrogate markers, expanded access and accelerated approval was shattered by our actions. The FDA staff looked shocked to hear such words coming from AIDS activists. They agreed to schedule a special meeting of the Antiviral Drugs Advisory Committee meeting in September to address our issues.

When Roche got a copy of our letter, they furiously faxed it to scores of activist organizations. A nationwide firestorm ensued. TAG became the most unpopular AIDS organization in the country. We became the target of vitriolic invective and personal abuse. Critics charged that we were trying to destroy Accelerated Approval. We were not – we were trying to save it, by forcing industry to live up to its part of the bargain – but the nuances of our position were quickly lost in the rumor mill.

Barron's magazine poured gasoline on the flames in mid-August when it ran a front-page article about the controversy, with extensive quotes and a picture of Spencer Cox, headlined, "DO WE HAVE TOO MANY DRUGS FOR AIDS?" That was not what Spencer said, of course, but the headline determined people's reaction to his presence in the article.

Time magazine duly weighed in a week later, with a photo of Spencer looking like a grunge singer loitering in a shadow-streaked Manhattan alley. For a few agonizing weeks, Spencer was the most hated AIDS activist in America.

We struggled to compile a clear statement of our policy position and assembled a monograph for the FDA hearing in September, *Rescuing Accelerated Approval: Moving Beyond the Status Quo*. The FDA hearing was a circus. Scores of activists harangued the committee, and vilified TAG, for two full days. We were clearly in a minority. David Feigal looked rather smug about this, though David Kessler listened intently to everyone.

Once we clarified that we were not opposed to Parallel Track and Accelerated Approval, the temperature dropped a bit. We worked with other community groups to demand that all three protease inhibitor developers, Abbott, Merck and Roche, develop Parallel Track programs for people with advanced AIDS. The programs that resulted were tiny, enrolling only a thousand patients each, but they gathered some useful safety data. The drug companies needed most of their small drug supply for their studies, and we were demanding that their studies be larger and longer.

After the crisis was over, we met with each of the protease sponsors. Derek Link even engineered a face-to-face meeting with Jürgen Drews, Roche's president of worldwide research. TAG maintained an ongoing critique of all the companies involved in the field, publishing another monograph, *Problems with Protease Inhibitor Development Plans*, at another FDA hearing in February 1995.⁵

In response to TAG's demands, Roche doubled the size of one of its pivotal efficacy trials, from 1,500 to 3,000. Abbott conducted a study we designed which randomized patients to Ritonavir or placebo, but allowed them to take any available nucleoside analogue as underlying therapy. This so-called "standard-of-care" control arm allowed patients maximum flexibility to choose among existing agents, while still rigorously measuring the efficacy of Ritonavir. Merck, certain that their drug was the best, was the most arrogant, and the least receptive to our ideas, until the ACTG finally agreed to do a large-scale study of Merck's Indinavir, ACTG 320, which would enroll 2,000 patients, largely subsidized with public funds.

By 1996, it was clear that, despite all the sound and fury, our campaign had been at least a qualified success. In February, Abbott Laboratories announced that its protease inhibitor Ritonavir plus nucleoside analogues reduced the risk of death in people with advanced AIDS by 50% over six months. Our standard-of-care control arm and our insistence on clinical endpoints had led Abbott to generate clearer clinical data on the efficacy of a new anti-HIV drug than any trial since the original Burroughs-Wellcome AZT study ten years before. The drug was fully approved overnight by the FDA. Abbott had gained a leap over Merck, which had only surrogate marker data and lacked enough drug to sell, though in a few weeks the FDA, which was now actively soliciting drug companies to apply for approval earlier than ever before, granted Merck Accelerated Approval for Indinavir. In May 1996, Roche released data from its study in advanced patients showing that even Saquinavir, the weakest of the protease inhibitors, prolonged survival in advanced patients when used in combination with a nucleoside.

Once the drugs were approved and on the market, thousands of people with failing immune systems started to take them. Many people experienced drops in their HIV levels of 99% or more, and corresponding CD4+ T cell rises. Some people left the danger zone of low T cells and maintained healthy levels for many months. The full duration of the antiviral

⁵ David Barr, Spencer Cox, Gregg Gonsalves, Mark Harrington, Derek Link, Michael Ravitch & Theo Smart, *Problems with Protease Inhibitor Development Plans*, for the National Task Force on AIDS Drug Development, 23 February 1995.

activity of the protease inhibitors is not yet known, since they are so new, but, thanks to TAG's advocacy, more is known about how to use them than was known about ddI, ddC or d4T at the time of their accelerated approval. Moreover, these drugs appear to be more powerful than the nucleosides, and attack a different viral target, so, when used in combination, they may provide the best control of HIV we have yet achieved, although resistance is likely to eventually appear.

There are several downsides to the protease inhibitors. Drug companies always say their experimental drugs are non-toxic, but each protease inhibitor has significant side effects, and they cannot be taken with many other common medications. Their rapid development has considerably complicated the medical management of HIV disease, and many further studies are required in order to figure out how best to use them. It remains unclear whether industry, NIH or anyone else will fund these urgently needed studies.

The protease inhibitor are also forcing a reimbursement crisis on public and private third party payers, comparable to the crisis posed by AZT's original price of \$10,000 per year. Each protease inhibitor costs between \$5,000-\$8,000 retail, and people are taking them alongside one or two nucleoside analogues. Already, many state AIDS Drug Assistance Programs cannot afford to cover these new drugs alongside already available ones, and the problem may only intensify in the coming years.

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ACTG 229: AZT/ddC/Saquinavir vs. AZT/Saquinavir vs. AZT/ddC

[May 1994]

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Results from ACTG 229, a randomized, 24-week, 302-patient study comparing AZT/ddC/Saquinavir (Ro 31-8959, the protease inhibitor) vs. AZT/Saquinavir vs. AZT/ddC, were released on May 31 [1994]. The analysis was written up by Roland Bassett, David Schoenfeld and Ann Collier for the ACTG 229 study team. Doses used were AZT 200 mg 3x/day, ddC 0.75 mg 3x/day, and Saquinavir 600 mg 3x/day. All participants had between 50-300 CD4 cells/mm³, and had received over 4 months of previous AZT. The principal endpoints were CD4 measurements and HIV load by PBMC co-culture. Analysis was by intent-to-treat. Only 10/302 patients (3%) took less than 80% of required study treatments.

ACTG 229: Results at 24 Weeks

	<i>AZT/ddC/ Saquinavir</i>	<i>AZT/ Saquinavir</i>	<i>AZT/ddC</i>
N	95	98	100
<u>Clinical Events + Toxicity</u>			
Major clinical events	1	6	4
Deaths on study	0	2	0
Severe/worse lab toxicity	27	31	30
Severe/worse clinical sign	5	11	12
Severe/worse lab tox. or clinical sign/symptom	31	50	37
<u>Immunologic Activity</u>			
CD4 cells returned to baseline @ 24 weeks	31%	37%	55%
CD4 NAUC	12.5±2.1	6.3±1.9	-0.15±2.1
25 CD4 cell or 25% rise	63%	53%	33%
50 CD4 cell or 50% rise	39%	28%	21%
<u>Virologic Activity</u>			
HIV PBMC reduced by 1 log	44%	9%	22%
p24 Ag reduced by 50%	61%	43%	28%
p24 Ag went negative	55%	30%	23%
Pl. viremia went negative	53%	44%	45%

“ACTG 229” Efficacy [sic] Analyses: Primary Analyses: CD4: The analysis of the log-transformed CD4 slopes showed a significant treatment difference ($p=0.005$) with the triple combination having a significantly greater slope than ddC/ZDV ($p=0.001$) but not Saquinavir/ZDV ($p=0.08$)...

Conclusions + Discussion: *Since ACTG protocol 229 was not designed with sufficient power to detect differences in clinical events, it is unknown if the favorable effect on surrogate markers seen with the triple combination in this 24 week study is associated with a delay in disease progression or enhanced survival. The beneficial effect on CD4 cell counts was transient in some patients, as demonstrated by downward trends in mean CD4 cell count after week 12. The suppressive effect of the triple combination on viral load as measured by HIV quantitative PBMC microculture was better than the double drug regimens, and appeared to be sustained for the duration of the study... There is a need to be cautious about comparisons between the double-drug regimens, because the study had insufficient power to rigorously allow comparisons. The type, severity, and frequency of adverse experiences appeared similar in the three regimens used in this double-blind study... The results of ACTG protocol 229 should be interpreted cautiously because it was a relatively small, short-term study, based upon laboratory endpoints. However, the results support the conclusion that a triple combination regimen containing Saquinavir, an orally-administered HIV proteinase inhibitor, has antiviral activity...*

“The clinical benefits of Saquinavir-containing regimens remain to be determined in future studies.” [ACTG 229 Executive Summary, May 1994]

Roche’s Currently Planned “Pivotal Efficacy Trials”

NVI426BA: Saquinavir alone vs. ddC alone vs. two doses of Saquinavir + ddC in AZT-experienced patients with CD4 50-300/mm³.

Endpoints: Primary: safety, tolerance and first AIDS-defining event or death; Secondary: Survival, Karnofsky, lab markers, quality of life, resistance.

Design: Randomized, double-blind, 48-weeks minimum follow-up, stratified by baseline CD4 >/<100.

Sample size: N=1200 patients, 300/arm, 240 evaluable/arm.

Comments: The control arm, ddC monotherapy, remains unvalidated in this population, it is smaller than that in BMS-019, the “pivotal” d4T trial, which many doubt is large enough to validate d4T (N=800, 400/arm).

SVI4804A: Saquinavir alone vs. AZT alone vs. two doses of Saquinavir + AZT in AZT-naive patients with CD4 50-300/mm³.

Endpoints: Primary: safety, tolerance, and first AIDS-defining event or death; Secondary: Survival, Karnofsky, lab markers, quality of life, resistance.

Design: Randomized, double-blind, 80-weeks minimum follow-up, stratified by baseline CD4 >/<100.

Sample size: N=1800 patients, 450/arm; 300 evaluable/arm.

Comments: The control arm, monotherapy, is standard-of-care in this population. The sample size/arm is similar to that of BMS-019, the “pivotal” d4T trial, which many doubt is large enough to validate d4T.

June 16, 1994

David Kessler, MD
Commissioner
United States Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Commissioner Kessler:

We are writing with reference to FDA's plans to regulate the development of a new class of anti- HIV therapies known as "protease inhibitors," and with specific reference to possible regulatory decisions regarding Hoffmann-LaRoche, Inc.'s Ro 31-8959 ("saquinavir").

As has been noted, both in meetings with you and your staff and in FDA Advisory Committee hearings, many of us are very concerned about the level of data that will be required for marketing approval of new classes of antiretroviral treatments. As people with AIDS/HIV, advocates and physicians [*sic*], we believe that people with AIDS are entitled to information about new therapies that is sufficient to make necessary risk/benefit analyses regarding their treatment. In regulating the first generation of antiretroviral drugs, many felt that a reduced evidential standard was appropriate, due to the absence of available treatments; now, however, we believe that the development of protease inhibitors offers a new opportunity to re-think this regulatory process in ways that will ensure reasonable access to new drugs, while producing clinically relevant information about their use. We would like to offer an approach to developing these therapies that combines access with the fundamental principles of clinical research. We believe that this approach can allow us to move as expeditiously as possible towards integrating the access and informational requirements of industry, FDA, and people with AIDS/HIV.

Specifically, we are concerned that Hoffmann-LaRoche, Inc. intends to apply for Accelerated Approval based on changes in CD4+ levels and virological markers observed in ACTG study #229. We feel that such an approval would penalize people with AIDS/HIV by setting an inappropriately low standard of evidential requirements that would govern the regulation of this entire class of therapies. We urge you not to invite Hoffmann-LaRoche 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.

Saquinavir, unlike d4T or ddC, is not yet an appropriate candidate for an accelerated NDA because it has not been studied for safety in a broad enough patient population for a long enough time, because Hoffmann-LaRoche's proposed follow-up studies are flawed, and because the use of surrogate markers to evaluate potential efficacy in ACTG 229 is completely untested in this class of therapies. The current ddC-controlled NV 14256A study does not use a validated control arm in this population and, like the projected AZT-controlled SVI4604A study, it lacks statistical power to determine probable magnitudes of treatment effect.

People with AIDS/HIV require access to life-saving treatment information. We have learned through difficult experience that we cannot depend on the goodwill of pharmaceutical industry sponsors to produce the information that is necessary to make life-or death treatment decisions. We believe that inadequate characterization of new drugs places PWA/HIVs in a deadly double bind: if a drug offers unmeasured, then people who refuse treatment may be losing opportunities for added health and life. If a drug is only as good as, or even worse than placebo, then patients taking it may be wasting time and money, and risking premature morbidity and mortality.

We are concerned too that, should Saquinavir be granted Accelerated Approval, future clinical investigators would then be ethically required to test new protease inhibitors against

Saquinavir, despite the lack of demonstrated clinical benefit. As we have seen with the nucleoside analogues, this would compound the problems of characterizing future therapies, and compromise the ability to obtain information about the utility of this entire class of therapies.

Instead of Accelerated Approval at the present time, we would suggest that sponsors of protease inhibitors combine strategies from past drug development processes in ways that are designed to produce maximal information at minimal cost. Instead of the traditional expanded access program, we would suggest a large, relatively simple comparing two doses of Saquinavir to placebo in all HIV-positive patients with ≤ 500 CD4+ cells/mm³ (see attached concept sheet). Such a study would not need to limit or exclude concomitant medications, other than excluding other protease inhibitors, and, indeed, would allow people in the study to receive any nucleoside analogue regimen they may wish to choose, in accordance with the 1993 PHS state-of-the-art guidelines. The study should be accompanied by a salvage protocol for patients who have failed on all standard therapies, or who have, less than 50 CD4+ cells/mm³. We believe that such a study, properly designed, could be faster and cheaper than the standard drug development process, could synthesize the twin goals of broad access and rapid, definitive answers, and could provide meaningful data on how best to use this new class of potential antiviral agents.

This issue is of particular concern in that Hoffmann-LaRoche has failed to honor previous agreements to conduct large-scale post-marketing studies to confirm the clinical efficacy of Zalcitabine [ddC]. Before FDA provides input to Hoffmann-LaRoche regarding an application for Accelerated Approval for Saquinavir, we ask that all parties consider this proposal. We are currently scheduling meetings with manufacturers of the various protease products, including Hoffmann-LaRoche, and would like to meet with FDA as soon as possible. Please [contact TAG] to set up a meeting in the coming weeks to further discuss these issues.

We now have a unique window of opportunity to plan prospectively a coherent, rapid and clinically useful development path for HIV protease inhibitors, and to learn from the lessons gained by five years of disappointing and contradictory research on nucleoside analogues. We must not let this opportunity slip by.

We look forward to working with you to resolve these issues.
Sincerely,

David Barr
Gay Men's Health Crisis
Spencer Cox
Treatment Action Group
Lynda Dee
AIDS Action Baltimore
Gregg Gonsalves
Treatment Action Group
Derek Hodel
AIDS Action Council
Mark Harrington
Treatment Action Group
Derek Link
Gay Men's Health Crisis
Bruce Schackman
Treatment Action Group

cc: Dr. Janet Woodcock
Dr. Robert Temple
Dr. Randy Wykoff
Dr. David Feigal

Letter from Rockville – TAGline 1:6, August 1994
(available on-line at <http://www.thebody.com/tag/augrockv.html>)

Another meeting with the (FDA) Commissioner, Rockville, MD, 11 July 1994. Bruce Schackman insisted that we all prepare overheads for our presentations, so we did. We took the train to Washington, D.C., and the Metro to Rockville. There we met Lynda Dee, resplendent in a peach-colored summer suit (with matching earrings, shoes and pocket book), and Ellen Cooper at the new AmFAR CBCT office across the street from DAIDS, for a pre-meeting. FDA officials met us in the Chesapeake Room in the Parklawn Building at 3:30.

David Barr pointed out that, as currently implemented, the Accelerated Approval regulations have failed to ensure that sponsors generate information about clinical utility post-marketing. People with HIV need access to information as well as to "un"-validated treatments. David Kessler took copious notes.

Gregg Gonsalves pointed out that the d4T hearing was badly programmed, and that the indication for which d4T was approved (salvage) is not the indication for which efficacy data may be forthcoming (second line). David Feigal pointed out that Bristol-Myers Squibb had promised to withdraw d4T from the market if BMS-019 does not prove clinical efficacy. "What if, as seems more likely, BMS-019 is inconclusive?" we queried. We don't want market withdrawal – we simply want greater certainty that even modest treatment benefit will eventually be discovered.

David Feigal said the FDA Antiviral Drugs Advisory Committee would meet in the fall to review the current status or surrogate markers, expanded access and Accelerated Approval. Gregg Gonsalves pointed out that the 1962 Kefauver amendments were still the law of the land. He showed Tom Fleming's analysis of the 16 randomized nucleoside trials that provided the basis for the 1993 state-of-the-art (SOTA) guidelines. In only two of the studies did CD4 rises correlate with a survival benefit. The overall predictability of CD4+ T-cell changes was 50 percent, no better than tossing a coin.

Spencer Cox showed overheads detailing problems with Accelerated Approval, and possible solutions. Surrogate markers (specifically, CD4) had proved disappointing. FDA should convene a periodic review of CD4 and other, newer potential markers, such as viral load measurements. FDA should require sponsors to hold a pre-phase II advisory committee hearing on their development plans if they were planning on applying for Accelerated Approval. The FDA could ensure a "black box" on the labeling noting that accelerated-approval drugs had not yet been clinically validated (as they did with d4T). Finally FDA might consider fining sponsors who failed to meet their post-marketing commitments. Commissioner Kessler questioned whether FDA had authority to do this.

Michael Ravitch presented some problems with the Inter-Company Collaboration (ICC) master protocol. David Feigal said that Merck's Ed Skolnick, at the National Task Force meeting in April, was receptive to randomization. Michael riposted that BW's David Barry had sent several condescending letters to the effect that randomization and controlling were unnecessary fetishes. David Kessler asked to see these letters, which we will forward to him. FDA was receptive to urging the ICC to design a better master protocol.

We discussed Roche's potential NDA for Saquinavir. FDA cannot disclose matters from ongoing discussions with pharmaceuticals. "We made it clear with Accelerated Approval that we were not seeking any less data, but only a different kind of data," Feigal said.

Wrapping up, David Kessler returned to the importance of the point about how Accelerated Approval needed to ensure the eventual development of answers, not only access, and indicated he would reflect on our concerns in a forthcoming article on Accelerated Approval. Speaking the next day to a reporter, Kessler noted that the community wants access to information, not just to potential new treatments.



TAG Position Statements
from *Rescuing Accelerated Approval: Moving Beyond the Status Quo*⁶

September 1994

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1. *What is TAG's position on Expanded Access?*

TAG supports the routine deployment by drug companies of expanded access programs for new treatments against HIV and its complications. After phase I data have demonstrated the preliminary safety profile and microbiological or immunological activity, TAG believes sponsors should make experimental treatments available through expanded access programs in the following circumstances: 1) in conditions where no approved treatment exists, to patients with that condition who are unable to enroll in controlled trials; and 2) in patients for whom standard therapy is not working, or who have become intolerant to standard therapy, for those patients unable to enroll in controlled trials. Depending on the condition, its standard of care, and the magnitude of patient need, TAG believes expanded access programs should encompass the spectrum from compassionate use/single patient IND to treatment IND and parallel track. In the latter cases, TAG believes useful efficacy information can be gathered by randomizing patients to different doses of the experimental drug, as was done with the Clarithromycin, ddC and d4T programs. **TAG also believes sponsors applying for accelerated approval must have conducted expanded access programs, to develop real-world safety data on the heterogeneous populations not studied in controlled trials, which will use the treatment after its approval.**

TAG believes that protease inhibitor developers should immediately begin planning and scaling-up production for an expanded access program for their compounds, which would open when they enter phase II/III studies. By sharing the burden between sponsors, each individual sponsor would have to contribute less than if only one sponsor were to provide expanded access, as Bristol-Myers did with ddl in 1989, giving Roche an opportunity to delay and deny meaningful expanded access. Industry must not deny expanded access to people with CD4<50, intolerant or failing approved therapies, as a gambit to whip up hysteria in the community for immediate accelerated approval.

2. *What is TAG's position on Accelerated Approval?*

TAG supports the Accelerated Approval regulations as written, but does not believe they have been fully implemented. FDA has not insisted on adequate and well-controlled confirmatory studies, and industry has not provided sufficient post-marketing information on whether

⁶ by Spencer Cox, Dennis Davidson, Gregg Gonsalves, Mark Harrington, Carlton Hogan & Rebecca Pringle-Smith: *Rescuing Accelerated Approval: Moving Beyond the Status Quo*, Treatment Action Group for the FDA Antiviral Drugs Advisory Committee, 12-13 September 1994, Rockville, Maryland

accelerated-approved drugs actually work. In order to ensure that industry fulfills its commitments to FDA, and to people with HIV who are taking approved but still unproved therapies, TAG believes the following steps must be taken: 1) FDA must have a public, pre-phase-II/III meeting to discuss any sponsor's development plan for a drug for which it envisions applying for accelerated approval; these meetings should provide an opportunity for the committee to assess whether the projected trials are likely to provide clear evidence of clinical benefit and to define what magnitude and duration of marker response(s) appeared likely, based on the most current data, to be associated with clinical benefit; 2) the sponsor must provide an expanded access program in the interim, for the reasons discussed above; and 3) the sponsor must have, underway at the time accelerated approval is granted, studies which are likely to demonstrate whether the drug prolongs health or life.

3. *What is TAG's position on Surrogate Markers?*

TAG believes that statistically significant changes in surrogate markers, developed from adequate and well-controlled studies, are acceptable indices for accelerated approval, provided that the conditions stated above are met, and that a study measuring clinical benefit is well underway at the time of approval and likely to provide a clear answer. TAG also believes that clinical efficacy studies are critical for validating and improving the use of surrogate markers, both for studying new drugs and, perhaps, eventually, using them to guide treatment strategies in primary care settings. Unless, however, clinical efficacy studies are conducted to validate and confirm surrogate marker effects, we believe that surrogate markers used alone to validate drugs are nothing but a biomedically-plausible superstition.

4. *What kind of evidence does TAG believe is necessary for FDA to approve protease inhibitors for treating HIV infection?*

As soon as protease inhibitors are proved, by adequate and well-controlled studies, to prolong disease-free time or life better than either 1) nothing at all, or 2) today's standard of care, we believe they should **be fully approved**. *If studies likely to prove this are well underway*, and adequate and well-controlled studies show a favorable combination of changes in CD4 levels and viral load, the latter preferably measured using new, more sensitive assays, we believe that a protease inhibitor could be considered for **accelerated approval**, provided that the spectrum of safety and toxicity is as well characterized as it was in the ddI, ddC and d4T expanded access programs. The safety data should include long-term observation of people with symptomatic disease on concomitant medications, in sufficient numbers to observe potential rarer side effects, like the pancreatitis seen with ddI and ddC. This again emphasizes the importance of the sponsor's having conducted a pre-approval expanded access program. Because of the potential for synergy between therapies targeting different viral proteins, we believe that protease inhibitors should be studied both as monotherapy and in combination with nucleoside analogues. If a protease inhibitor proved "equivalence" with an approved nucleoside analogue, for example, ddC, we would not know whether that was, in fact, better than nothing at all. Whether AZT/Saquinavir is, in fact, equivalent to AZT/ddC, for example, is not a question which we think is worth asking, or easy answering. Therefore, we are most interested in the question: does a protease inhibitor, added to the best current therapeutic strategy, which is the standard-of-care outlined in the 1993 state-of-the-art (SOTA) guidelines, improve outcomes when compared with standard-of-care alone?

Gregg Gonsalves + Mark Harrington, 9.1.94

FROM: PROBLEMS WITH PROTEASE INHIBITOR DEVELOPMENT PLANS

by Derek Link, Spencer Cox, Gregg Gonsalves, Derek Link,
Michael Ravitch, and Theo Smart, for TAG & GMHC

edited by Mark Harrington

23 February 1995

*

After attending a meeting at which the largest drug company in the world presented its meager plans for protease development, I wondered how those doctors felt about their work. Do they believe that their trials are sufficient to answer critical questions about their drug? Does the FDA believe that sufficient data exist to approve drugs on the basis of changes in viral load? If not, what are they doing about it? Is the NIH comfortable about having no role at all in this effort, one of the most important aspects of AIDS drug development? . . .

Some individuals within the community of which I am a part, in their desperation, seem willing to forego any standards whatsoever, just for the opportunity of putting a new pill into their mouths. I, for one, am not willing to accept a standard of care based on desperation. I still want to know if the pill works. Not just for myself, but because there are tens of millions of people who will be faced with making these difficult treatment decisions long after I am gone. They will want to live long, productive lives. They will want to believe that when their doctor gives them medicine, it will work. We have a responsibility to them. A responsibility to learn from our mistakes in the past. A responsibility to look past our own desperation, ambition or greed. A responsibility to the public health.

*Early access and accelerated approval of protease inhibitors must be part of any development plan. Let me say that again, lest someone did not hear it the first time – **early access and accelerated approval of protease inhibitors must be part of any development plan.** . . . However, just as I am desperate for the earliest access possible to these drugs, I am equally desperate to know what a moderate and time-limited treatment-induced reduction in viral load means, how best to approach the problems of drug resistance, and how to obtain meaningful information about using these drugs in combination with the existing standard of care. Very few other parties in this debate seem committed to obtaining this information. If that is not true, then prove it. Begin here, at the place where all the relevant players are represented. If not here, then where? If not now, then when?*

– from the Introduction by David Barr

Update & Commentary on Protease Inhibitor Development Plans

Roche INVIRASE™ Saquinavir

by Mark Harrington

(February 1995)

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(available in part on-line at <http://www.thebody.com/tag/problems.html>)

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Background

ACTG 229, a randomized comparison of AZT/Saquinavir and AZT/ddC to AZT/ddC/Saquinavir showed that the three-drug regimen conferred modestly better virologic and immunologic effects than the 2 two-drug regimens (which were virtually indistinguishable) in 302 patients enrolling with 50-300 CD4 cells/mm³ and over 4 months' previous AZT use. The sponsor, Hoffman-LaRoche, conferred with FDA in summer 1994 over whether these results justified an application for accelerated approval. Since only 99 patients received the three-drug regimen, and there was no large-scale safety data and just one small phase III trial underway, the FDA demurred, and Roche mounted an extensive phase III program.

Phase III Development Plans

Roche is the only HIV protease inhibitor developer whose phase III program is well underway. Its trials are the largest designed to date, and it is the only company to have committed to a meaningful (N=4,000) expanded access program, which is slated to begin in the third quarter of 1995. There are two pivotal studies. Both were redesigned last summer, partially in response to concerns raised by us and others. The first-line trial was complicated and enlarged, and the second-line trial simplified and shrunk. These changes are ample evidence that Roche, FDA and others with a stake in the process, including the community, are struggling for a resolution to many complex issues: How should protease inhibitor trials be designed? How should they be controlled? How large should the trials be? What level of treatment effect should the trials seek to distinguish? Unfortunately, there has never been a systematic discussion of the comprehensive development of the protease inhibitors as an entire class. Instead, questions with significant public health consequences for all people living with HIV are being addressed individually and privately by Roche, Merck, Abbott and other protease developers. The time has come to evaluate protease inhibitor development as a whole, as a single class of new drugs, the evaluation of which poses common dilemmas and problems.

- **First-line therapy.** Roche's SV14604C is a four-arm, 80-week study enrolling 3,300 antiretroviral-naive participants with CD4s between 50-300; they are being randomized to AZT vs. AZT/ddC vs. AZT/Saquinavir vs. AZT/ddC/Saquinavir. Primary endpoints include time-to-first AIDS-defining-event or death, and secondary endpoints include viral burden, CD4 levels, emergence of viral resistance and syncytium-inducing phenotypes, weight gain, Karnofsky performance status and quality of life. 800 participants will receive more intensive virological monitoring. A planned interim surrogate marker analysis will be submitted to FDA whenever Roche is ready to apply for accelerated approval (probably in the third quarter of 1995).
- **Second-line therapy.** NV14256B is a three-arm, 48-week study randomizing HIV-infected patients with between 50-300 CD4 cells who received previous AZT therapy or are AZT-intolerant to ddC monotherapy, ddC/Saquinavir or Saquinavir alone. This is

both a pre-marketing validation study for Saquinavir and a postmarketing validation study for ddC (HIVID™ brand zalcitabine). Participants will be stratified by baseline CD4 levels ($>/<100$; only 25% of subjects will be in the lower stratum. Primary and secondary endpoints are the same as in SV14604C. A planned interim analysis will occur when 150 patients per treatment group (half of the study's target enrollment) have received at least 16 weeks of treatment. Presumably, the surrogate marker results of this analysis, if they resemble those seen in ACTG 229, will be bundled off by airmail to Rockville for consideration by FDA for accelerated approval. The impact of accelerated approval on the ability to complete the two pivotal Roche trials remains unclear.

- **Advanced patients: expanded access.** Roche has committed to opening, in the third quarter of 1995 [*note: just before its FDA approval hearing on November 5!*], an expanded-access program for HIV-infected persons intolerant to or refractory to approved and available therapies (the nucleoside analogues). Initially drug will be available for 4,000 participants. We salute Roche for responding positively to our request for a salvage protocol in July 1994, and the community consensus statement on a Saquinavir Parallel Track from November 1994. Roche is considering enrollment through a lottery process. Hopefully Roche will take steps to ensure that people with the greatest need (or at greatest risk of death) will receive priority treatment.

Comments

Clearly, of the two studies, the larger, first-line therapy study appears likelier to lead to a clear answer about clinical benefit. SV14604C was designed to have a 90% power to detect an increase in event-free rates over 80 weeks from 75% to 82.5% (a relative reduction of 30%) between two treatment groups, or from 82.5% to 89% (37% relative reduction). Differences of this magnitude have yet to be seen in first-line active-controlled studies (with the exception of ACTG 114). With 750 participants per arm, this study is certainly larger than previous active-controlled antiretroviral efficacy studies, however, and we can certainly salute Hoffman-LaRoche for at least moving (if not far enough) in the right direction towards larger studies which are more likely to detect moderate but clinically meaningful treatment differences.

The second-line study, NV14256B enrolls a population similar to that which enrolled in ACTG 155, substituting Saquinavir for AZT in its design, and a similar (N=900) sample size. As we all remember, ACTG 155 showed that, overall, there was no difference between AZT alone, AZT/ddC or ddC monotherapy in delaying progression, but that AZT/ddC was 50% more toxic overall. The trial lacked the power to make finer distinctions, though unplanned subset analyses suggested that there might be additional benefit in people with $CD4 > 150$, and additional harm in people with $CD4 < 50$, to combination vs. monotherapy. Surrogate marker changes on Saquinavir-containing regimens in ACTG 229 do not suggest that Saquinavir will outperform AZT in ACTG 155, and so the ability of NV14256B to provide clear evidence of clinical benefit appears slender. The study designers assumed, based on event rates from ACTG 116B/117, 155 and CPCRA 002, that 12-month progression-free rates on ddC monotherapy would be 75% (25% would progress in 12 months). They powered this study to detect an increase in progression-free rate from 75% to 88%! This would amount to a relative reduction in event rate of 52%, which could be detected with 90% power, and assuming a 20% dropout rate. It strikes us as exceedingly naive and over-optimistic to plan for such a dramatic clinical difference when the only second-line study to show clinical benefit to date, ACTG 116B/117, showed only a relative difference of 15% in time-to-AIDS event or death. The tragedy here is that if a much smaller benefit (or harm) occurs, this trial will be unable to measure it, and we will be plunged back into the disputatious world of post hoc subset trend analysis.

NDA at a Glance: INVIRASE™ Brand Saquinavir

Who: FDA Antiviral Drugs Advisory Committee
What: INVIRASE™ brand Saquinavir (Hoffmann-LaRoche & Co.) at 600 mg t.i.d.
Where: Gaithersburg, Maryland
When: 6 November 1995
Why: For the treatment of advanced HIV infection in adults for:

- **Combination therapy** with approved antiretroviral agents
- **Monotherapy** for those who cannot tolerate approved antiretroviral agents

How: Through the FDA's accelerated approval regulations using surrogate marker data (CD4 changes and plasma viral RNA changes) from five phase I and II studies:

	<u>Site</u>	<u>N</u>	<u>Dose(s), Regimen(s)</u>
AZT-naive			
013328	UK	49	SQV 75, 200, 600 mg tid
V13330	Italy	92	SQV 75, 200, 600 mg tid ± AZT
AZT-experienced			
V13329	France	61	SQV + AZT?
NV14255/ACTG 229	USA	295	AZT/SQV/ddC v. AZT/SQV v. AZT/ddC
NV14256	USA	423 ⁷	ddC v. SQV v. ddC/SQV

Safety, pharmacokinetics and antiretroviral activity as measured by CD4 cell changes and plasma viral burden (RNA PCR) changes are based on complete data from the first four studies and interim (16 week) data from NV14256⁸.

UK and Italian phase I studies. Saquinavir monotherapy has antiviral activity at 600 mg tid, the proposed licensed dose. It has less activity at 75 or 200 mg tid, and slightly more at 3600 or 7200 mg/d (the Stanford study presented at ICAAC). At 600 mg tid in monotherapy CD4 cells rose by about 30 in AZT-naive patients (baseline ~200), compared with plus 20 on AZT, minus 10 on 200 mg SQV, minus 25 on 75 mg SQV. Viral RNA, by contrast, fell by about 0.5 log on AZT and by only 0.3 log on SQV 600 mg tid monotherapy in this naive population. Dr. Salgo commented, "Saquinavir appears equivalent to AZT in a naive population and to ddC in an experienced population." Participants in Stefano Vella's preliminary combination study had superior 16-week CD4 rises on high-dose (600 tid) SQV/AZT averaging about 50 cells (baseline 200). Viral RNA levels fell by about 1.6 logs at 2-4 weeks and remained 0.8 log below baseline at 16 weeks on the combination, which was superior to AZT alone, which was superior to SQV alone. 87% of those on AZT/SQV had both a CD4 rise and an HIV RNA drop, versus 69% on AZT alone and 47% on SQV alone. Results from ACTG 229, a randomized, 24-week, 302-patient study comparing AZT/ddC/Saquinavir (Ro 31-8959, the protease inhibitor) vs. AZT/Saquinavir vs. AZT/ddC, were released in May 1994. All participants had between 50-300 CD4 cells/mm³, and had received over 4 months of previous AZT. The principal endpoints were CD4 measurements and HIV load by PBMC co-culture. Analysis was by intent-to-treat.

⁷ The NDA database from NV14256 consists of data from 423 patients who completed 16 weeks of follow-up, although the total size of the study is around 900.
⁸ SV14604C, the European-American first-line study (N=3,300, AZT vs. AZT/ddC vs. AZT/SQV vs. AZT/ddC/SQV; randomization to AZT alone will stop due to 175/Delta; it's about half accrued) has insufficient interim data to present.

	<u>AZT/ddC/SQV</u>	<u>AZT/SQV</u>	<u>AZT/ddC</u>
N	95	98	98
Clinical Events + Toxicity			
Major clinical events	1	6	4
Deaths on study	0	2	0
Severe/worse lab tox. or clinical sign	31	40	37
Immunologic Activity			
CD4 cells @ baseline @ 24w	31%	37%	55%
25 CD4 cell or 25% rise	63%	53%	33%
Virologic Activity			
p24 Ag went negative	55%	30%	23%
Plasma viremia went negative	53%	40%	45%

Extended treatment with Saquinavir, AZT and ddC-containing regimens (ACTG 229 follow-up, ICAAC "95 presentation #173). Ann Collier of the University of Washington in Seattle presented long-term follow-up data from ACTG 229, the 302-patient study comparing AZT/ddC to AZT/Saquinavir and AZT/ddC/Saquinavir. Over its first six months, there were modestly greater CD4 and viral load changes in the triple-drug arm compared with the double-drug arms, with no measurable clinical differences. 94% of participants completed the initial 24-week study and 244/302 (82%) of these completed an additional 24 weeks of follow-up; 218/302 (73%) remained on study until completion.

ACTG 229 Follow-Up: Data at Week 48

CD4 percentages returned to baseline in the triple combination group at week 44. C.J. Hopper and colleagues also presented a poster attempting to correlate CD4 changes with viral burden changes in 201 patients from ACTG 229. 107/201 patients had no significant decrease in RNA or infectious units area under the curve (AUC). The median CD4 AUC was +4.4 cells/il. 51 had a decrease in RNA AUC ≥ 2.5 log and 7 had a decrease in IUPM AUC ≥ 0.5 log. The median CD4 AUC increased by 16 and 16 cells/il in these groups. 36 patients having decreases in both RNA and IUPM AUC had a median increase in CD4 AUC of 48 cells/il ($p < 0.001$). "The trend of CD4 cell count rise correlating with RNA suppression reached statistical significance in all three treatment arms ($p \leq 0.038$), but only patients on triple therapy had an association between increased CD4 count and decreased IUPM ($p = 0.043$)... Patients with the greatest decrease in viral load, especially those with drops in both plasma viremia and cellular infectivity, had the greatest and most enduring increase in CD4 count." (1152).

Higher doses of Saquinavir (LB-5). Jonathan M. Schapiro of Stanford presented an open-label study of two higher doses of Saquinavir. 20 patients each were randomized to receive 3600 or 7200 mg Saquinavir daily for 24 weeks. Mild liver function test elevations, confusion, GI upsets were reported at the higher dose. CD4 counts rose by an average of 72/mm³ at 4 weeks and by 121 at 20 weeks. Two critical mutations at codons 48 and 90 are associated with the development of resistance to Saquinavir. 13/40 developed the 48 or 90 mutation over the course of the study, with the suggestion but not proof that the higher dose delays the emergence of the mutation(s) as opposed to the lower dose.

Resistance to Saquinavir (I174). L48V and L90M are two mutations in the protease gene which clearly induce a Saquinavir-resistant phenotype, however Saquinavir-resistant HIV remains susceptible to six other protease inhibitors. In a European study at 25 weeks 50% have low-level resistance and the rest develop it by 12 months. In the three-drug arm of

ACTG 229 only 22% had resistance at one year. **Note:** the codon 48 and 90 mutations appear to confer resistance to the Agouron protease inhibitor now in phase I-II studies.

Safety. Side effects appear minimal and are mainly limited to asymptomatic rare LFT elevations and symptomatic GI distress.

Bioavailability. Current bioavailability is about 4%. Roche's "enhanced oral formulation" is exiting phase I bioequivalence studies.

Ongoing & planned studies. Roche did not present data at the 10.24.95 TAG/GMHC meeting on its ongoing NV14256 second-line or SV14604 first-line studies, results of which will be in by 1996 and 1997 respectively. Their expanded access program (current N=1,500) is too new for substantial safety data to have been generated. They are planning to work with Abbott and Merck respectively on combination studies with ABT-538 and with Indinavir sulfate. They have no planned interaction studies for the Rifamycins and the azole antifungals; however, Rifamycins appear to speed up Saquinavir metabolism by 40-80% (for Rifabutin and Rifampin respectively); Ketoconazole raises Saquinavir's bioavailability by 150%. Other azoles probably do as well. Grapefruit juice raises it too, not as much.

Unanswered Questions: Will Saquinavir enhance the likelihood of resistance to Indinavir (in which the L90M mutation is "necessary but not sufficient")? When will they develop a tolerable pediatric dose? Will they commit to meaningful pharmacokinetic/drug interaction studies? When will their "enhanced oral formulation" become available? What will be the price? Will third-party payors reimburse for expensive new antiretrovirals? Will a "reformed" Medicaid/Medicare? How much will combination protease/nucleoside regimens cost?

– **Mark Harrington**
TAG, 10.24.95



Position Paper on Accelerated Approval for INVIRASE™ brand Saquinavir

by

**Mark Harrington, Policy Director
Treatment Action Group
7 November 1995**

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In September 1994 the Treatment Action Group spelled out the following conditions as necessary for our support of an accelerated NDA for an HIV protease inhibitor⁹:

1. Adequate and well-controlled clinical endpoints studies are well underway and likely to show whether the drug can prolong disease-free time or survival;
2. Adequate and well-controlled studies are complete or well underway and demonstrate a favorable combination of changes in CD4 levels and viral load;
3. The safety profile is adequately characterized and acceptable; and
4. The sponsor provided an expanded access program.

One year later, Hoffmann-LaRoche Inc. is the first sponsor to apply for accelerated approval of a protease inhibitor, INVIRASE™ brand Saquinavir, and is asking for two indications at 600 milligrams (mg) three times daily (t.i.d.):

- **Combination therapy** for use with approved antiretroviral agents [the nucleoside analogues] in adults with advanced HIV infection, and
- **Monotherapy** for use in adults with advanced HIV infection who are intolerant to or failing on approved antiretroviral agents.

We believe that Roche has substantially met the conditions we laid out one year ago for accelerated approval for these two indications:

1. **Clinical endpoint studies.** Two large ongoing studies, NV14256 and SV14604, are examining whether Saquinavir-containing regimens are superior to today's nucleosides alone. NV14256, with three arms and about 900 participants, will be about as powerful as ACTG 116B/117, which showed ddl superior to AZT as second-line therapy. SV14604, with four arms and about 3,200 participants, will be more powerful than ACTG 175, which showed ddl and two combinations superior to

⁹

Spencer Cox, Dennis Davidson, Gregg Gonsalves, Mark Harrington, Carlton Hogan and Rebecca Pringle Smith for the Treatment Action Group, *Rescuing Accelerated Approval: Moving Beyond the Status Quo*, a report to the FDA Antiviral Drugs Advisory Committee, 12-13 September 1995, Silver Spring, Maryland.

AZT alone as first-line therapy. We believe these studies are likely to demonstrate whether Saquinavir confers clinical benefit.

2. **Surrogate marker studies.** Data from uncontrolled phase I studies and from the randomized ACTG 229 study demonstrates that Saquinavir has favorable effects on CD4 counts and less dramatic but still favorable effects on viral load. We have not seen today's interim look at NV14256 which will strengthen or weaken the conclusions from these earlier studies. Assuming that these new data do not contradict the earlier studies, we believe these surrogate marker benefits may confer a clinical benefit.
3. **Safety profile.** Saquinavir shows little acute toxicity. Long-term data in diverse populations remains inadequate, yet the short-term risk ratio is clearly low.
4. **Expanded access program.** We are pleased that Roche eventually met the community's demand for an expanded access program, one which is substantially larger than those of its competitors, but we are also disappointed that the expanded access program did not begin early enough for safety data to be available for review by the FDA and this committee here today. We are also disappointed that Roche did not avail itself of the opportunity to compare outcomes on those receiving Saquinavir under the lottery and those who applied but did not receive the drug. A randomization occurred, but no comparative data will be gathered. This is a regression from the dose-randomizations which took place with ddC and d4T. We hope future expanded access programs will be randomized, and if a lottery is necessary due to supply problems, that comparative survival will be measured.

Proposed indication for Saquinavir

Dose & Formulation. Due to competitive concerns, Roche has submitted what may be a suboptimal dose and what is definitely a suboptimal formulation. This raises troubling issues for the post-marketing period, but does not eliminate the demonstrated surrogate marker benefits.

Population. Roche is, appropriately, asking for approval in the groups for which it has completed or ongoing clinical endpoint studies, those with advanced HIV disease, mostly under 300 CD4 cells. **Regimen.** Roche has mainly studied Saquinavir along with AZT, ddC or both. However Roche is asking for approval for use with any approved antiretroviral, presumably including ddI, d4T and (soon) 3TC. These combinations have not been adequately studied, but reflect the real-world conditions under which Saquinavir is likely to be used. FDA should mandate formal studies of these combinations and interactions as part of the post-marketing package.

Resistance and cross-resistance. Because evidence and opinion are contradictory, we believe the initial labeling indication for Saquinavir must include a prominent warning about the possibility of resistance and cross-resistance to other protease inhibitors.

Current issues and future directions

Obviously many outstanding questions remain about how to optimize the use of Saquinavir.

- **Pediatric studies.** We are disappointed that problems in developing a palatable pediatric formulation have delayed the initiation of safety and activity studies in infants and children. *Developing and studying a formulation for children with HIV infection must be among the highest priorities for Roche in the post-marketing period.*
- **Formulation.** Saquinavir is poorly bioavailable (4%). Roche is working on an "enhanced oral formulation" but this is not yet ready. *An enhanced formulation must be rapidly developed.*

- **Dose.** The optimal dose is not yet clear. The Stanford study suggested that higher doses may have more dramatic effects on surrogate markers and may delay the emergence of resistance. ***The optimal dose of Saquinavir needs to be defined.***
- **Resistance and cross-resistance.** There are conflicting reports about whether Saquinavir use induces mutations which may decrease the antiretroviral efficacy of other protease inhibitors such as the Merck and Agouron compounds. Roche must work with academic virologists and with other protease inhibitor sponsors to resolve these issues around the virological and clinical significance of resistance and cross-resistance. ***We believe the initial labeling for Saquinavir should include a prominent box warning that use of Saquinavir may limit the clinical and virological utility of future protease inhibitors, and that physicians and patients must be educated about this possibility in Roche promotional materials.***
- **Combination protease therapy.** There is also the possibility of antiviral synergy between protease inhibitors, e.g., between Saquinavir and either Indinavir or Ritonavir. ***The sponsors should work together to define optimal combination or sequential regimens.***
- **Optimizing clinical utility of protease inhibitors.** Currently neither NIH nor industry have developed adequate infrastructure to define the answers to such questions as 1) when is the optimal time to initiate antiretroviral therapy; 2) what are the optimal antiretroviral regimens or treatment strategies; 3) how can we maximize clinical benefit, minimize expense and toxicity and rationally use the plethora of antiretroviral agents which we will soon have at our disposal? ***NIH, industry and the community should work together to develop structures capable of answering questions about optimizing clinical benefit.***
- **Price and access to underserved populations.** As a chemically new and complex set of compounds, the HIV protease inhibitors are likely to be marketed at prices higher than those now seen with current nucleosides. We are concerned about the impact of an excessive price for Saquinavir and other protease inhibitors on third party reimbursement, particularly in an era when the social safety net (Medicaid, Medicare, Ryan White, and state AIDS drug assistance programs), upon which the great majority of people with HIV depend, is under unprecedented attack. FDA approval will be meaningless if protease inhibitors are priced beyond the ability of programs upon which the vast majority of people with AIDS are dependent are unable to afford them, or are forced to make unacceptable choices between expensive antiviral regimens versus life- and health-extending opportunistic disease treatment and prophylaxis. ***We strongly urge Roche to set an example by pricing Saquinavir at an acceptable level and avoid intensifying a reimbursement crisis for people with HIV.***
- **Continued availability under expanded access in countries lacking accelerated approval.** Many countries, e.g., in Europe, will not necessarily approve Saquinavir just because it was approved in the U.S.A. based on surrogate markers. ***Roche should undertake to assure that an adequate supply of the drug will remain available under expanded access in countries which will await evidence of clinical efficacy before approving Saquinavir.***
- **Drug interaction studies with commonly-used HIV and AIDS treatments.** Surveillance through expanded access will be inadequate for assuring that there are not harmful interactions between Saquinavir, other antiretrovirals and anti-opportunistic disease drugs. ***We urge Roche to conduct pharmacokinetic interaction and activity studies with Saquinavir and the nucleosides, other protease inhibitors, and other commonly-used AIDS treatments, particularly the rifamycins (Rifampin and Rifabutin), the azoles (Fluconazole, Itraconazole, Ketoconazole, etc.), as well as with other commonly used medications such as birth control pills and methadone.***

Potential post-marketing clinical efficacy studies

We believe Roche should commit to post-marketing studies designed to 1) confirm its currently sought indication by demonstrating clinical benefit with other nucleosides, e.g., ddI, d4T and 3TC and 2) extend its application to people with higher CD4 counts. Because it is not randomized the current expanded access program will tell us little about Saquinavir's efficacy with other nucleosides. Among the most interesting populations to study would be those with medium CD4 counts (between 200-500) using first- or second-line therapy. Possible study designs include:

1. **An early versus late trial.** People could start, switch or stay on any nucleoside therapy they chose, and be randomized to start Saquinavir immediately or after a CD4 drop, a viral load increase or the development of symptoms;
2. **A viral-load switchpoint trial.** People could be randomized to start Saquinavir (used with any nucleoside at will) immediately or when their viral load rises past 150,000 copies and by more than three times baseline;
3. **Standard-of-care alone versus SOC plus Saquinavir.** People concerned about possible cross-resistance could be randomized to start Saquinavir (used with any nucleoside at will) or placebo (used with any nucleoside at will).

These study designs could be adapted for any of the new antiretrovirals currently up for approval, particularly 3TC, and could also be adapted for the protease inhibitors. Insurance could cover the underlying standard-of-care nucleosides, and the sponsors (Roche or Glaxo) could cover the experimental drug, placebo and data gathering costs. Studies could take place in community-based settings, public health clinics, through HMOs or in the approximately 1,200 doctors' offices used to carrying out expanded access programs. Eventually, protease monotherapy versus combination or sequential therapy approaches should also be studied.

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**Giving Away the Farm:
How Corporate Cynicism, Savvy Schmoozing and Relentless PR
Paved the Way to Unqualified Approval for Two New Antiretrovirals**

by Spencer Cox

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(TAGline 2:11, December 1995; available at <http://www.thebody.com/tag/dec95b.html>)

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The FDA's Antiviral Drug Products Advisory Committee met on November 6-8 in a marathon session to consider accelerated approval for Glaxo Wellcome's Epivir brand lamivudine (3TC) and Hoffmann-La Roche's Invirase brand saquinavir, as well as full approval for Bristol-Myers Squibb's Zerit brand stavudine (d4T). TAG was there, getting all the data and dish. Spencer Cox prepared this report.

Bought and Paid For

On Tuesday, the FDA committee considered approval of an accelerated NDA for *Invirase* brand saquinavir, Hoffmann-La Roche's less-than-stellar first entry into the protease sweepstakes. The NDA requested approval of saquinavir for use in combination with any approved nucleoside analogues in adults with advanced HIV infection, and for use alone in adults with advanced HIV infection who are intolerant to or failing approved therapies.

The company presented data from uncontrolled phase I studies, as well as from two phase II studies: ACTG 229, a randomized trial comparing saquinavir+AZT vs. AZT+ddC vs. AZT+ddC+saquinavir; and interim data from NV14256, a study of 900 antiviral experienced patients comparing saquinavir vs. ddC vs. saquinavir+ddC. All told, saquinavir was pretty disappointing. As monotherapy, the surrogate marker responses were roughly comparable to AZT; in combination with AZT, the surrogate responses were not much better than what we've seen with AZT+ddC. Roche is currently conducting two studies which hope to provide clinical confirmation of saquinavir's usefulness: the first being simply clinical follow-up of the NV study; and the second, a study called SV14604, which will follow 3,200 antiviral naïve patients for 80 weeks, comparing AZT vs. AZT+ddC vs. AZT+saquinavir vs. AZT+ddC+saquinavir.

Some of saquinavir's disappointing surrogate marker responses (and also the relatively good toxicity profile) may be due to the drug's poor bio-availability. As currently formulated, only 4% of the drug makes it into the blood, which understandably prompted the committee to pose the question, "Why is Roche coming to us now with a drug that isn't even bio-available?" Furthermore, the committee was concerned that, while Roche was seeking an indication for saquinavir to be recommended for use with combinations of any of the approved nucleoside analogues, it had conducted drug interaction studies with only AZT and ddC. Finally, the conflicting claims from Merck and Roche regarding possible cross-resistance between their protease inhibitors have not yet been resolved. TAG supported accelerated approval of both combination and monotherapy indications for saquinavir, but the committee recommended approval only for use in combination. The FDA granted saquinavir licensure on December 5, and it was in pharmacies the following day—at an annual price tag of around \$6,000.

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CYNICAL SWISS SAQUINAVIR SCAM: ROCHE ADMITS LICENSED DOSE SUBOPTIMAL

How Many Became Cross-Resistant in Roche's Rush to Market?

New Formulation Gets Blood Levels Eight-fold Higher, Safely

Why Would the Weakest Protease Inhibitor Cost the Most?

Company Pulls "Strategy" Ads After Community Balks

Can SQV Soft Gel Caps Save the Day?

by Mark Harrington

7 June 1997

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(available on-line at <http://www.aidsinfonyc.org/tag/tx/sqv.html>)

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"Cynical", "greedy", "manipulative", "opportunistic", "penny-pinching", "short-sighted", "slipshod" – do these words come to mind when you think of Hoffmann-LaRoche's AIDS drug development efforts? They should. Examples of such behavior are legion, from the fiasco that was ddC to the joke that is the current formulation of saquinavir to the curious decision by the Basel-based pharmaceutical giant to drastically curtail development of valganciclovir, the oral ganciclovir prodrug which offered the hope for finally being an effective prophylaxis for cytomegalovirus (CMV) disease. As one high-placed Federal official noted (off the record, of course) of the latter decision, "Roche finally has a decent drug, and they're thinking of dropping it." Roche's HIV program gives the "ethical" pharmaceutical industry a bad name.

Saquinavir, like ddC, is the most potent drug of its class – in vitro. However, only 4% of the drug gets into the bloodstream. Hoffmann-LaRoche was in such a hurry to get its drug licensed as the first protease inhibitor that it never bothered doing the dose-ranging studies that could have defined a maximum tolerated dose (MTD) for saquinavir.

I was a member of the ACTG's Primary Infection Committee when Roche approached them to conduct the phase II study, dubbed ACTG 229. The dose chosen was 600 milligrams (mg) thrice daily, based, they claimed, on three European phase I studies, or, as others thought, on a limited drug supply which made higher doses impractical – or not worth Roche's investment. While the Primary Infection Committee was never known as a bastion of open scientific debate, ACTG 229 was swaddled in a secrecy unusual even for them. Roche declined to present the results of its phase I studies to the committee as a whole. Rather, they allowed Thomas Merigan of Stanford University and Ann Collier of the University of Washington at Seattle to take a peek at the alleged phase I virological response to saquinavir.

The study would take place in AZT-experienced patients, then the favorite population for trials of new antiretrovirals (remember ACTG 155?). They would be randomized to receive either AZT and ddC, AZT and saquinavir, or AZT, ddC and saquinavir. This was one of the first of the so-called "incestuous combination" studies recently pilloried by Joep Lange, in which a company's own drugs are studied together as much as possible, regardless of the scientific rationale for doing so.

Preliminary review of the study design by the Division of AIDS (DAIDS) and Harvard's Statistics & Data Analysis Center (SDAC) raised several concerns, which I mentioned to Dr. Collier (the principal investigator of ACTG 229) in a letter on 30 September 1992:

I remain perplexed about the current design of ACTG 229. In particular, I share the CTRC's concern "about the selection of 600 mg tid as the dose of Ro 31-8959 [saquinavir] since there is no established maximum tolerated dose" [NIAID Clinical Trials Review Committee letter, 27 August 1992]. Doses as high as 1200-1800 mg tid have been tested in HIV-negative patients and found to be safe... but people with HIV have only been given doses up to 600 mg tid. I would concur with the CTRC that "the need for the pharmaceutical sponsor to be forthcoming with data from their European trials" is pressing as we proceed towards opening ACTG 229...

I became even more concerned when I read David Schoenfeld's SDAC review. His bottom line was that "the proposed study will not be able to detect whether Ro 31-8951 has moderate activity."

Needless to say, the ACTG brushed aside the concerns of statisticians and activists and conducted the study as Roche wished it to. 300 AZT-experienced individuals were enrolled and followed for 18 months. By June 1994, Roche had detected the surrogate marker response it hoped for (triple drug combination proved superior to either two drug combination as measured by CD4 cell response and, less impressively, by viral load). As Schoenfeld predicted, the study failed to show whether saquinavir was any more potent than ddC, the weakest of the nucleoside analogues in vivo. Undeterred by this minor annoyance, Roche promptly petitioned the FDA to consider an accelerated new drug application (NDA) for saquinavir.

Worried by the precedent this would set for the protease inhibitors as a class, TAG – along with representatives of Gay Men's Health Crisis and AIDS Action Baltimore – then wrote to FDA Commissioner David Kessler requesting that accelerated approval for saquinavir be placed on hold until a full and open public debate could take place to assess how much data would be required for accelerated approval of protease inhibitors, and how post-marketing confirmatory studies should be designed.

In the controversy that ensued, Roche quietly agreed to double the size of its pivotal efficacy trials, thereby increasing their ability to determine whether saquinavir provided any clinical benefit. Unfortunately, the study that was eventually to provide such evidence – Roche NV14256B – compared saquinavir to ddC to the combination in AZT-experienced patients. Since the role of ddC in this population is far from clear, and its benefit dubious in any population, such a control arm must be regarded as questionable. Nonetheless, to no one's surprise, the combination of these two drugs, each the weakest in its class, proved to be more potent than either one alone.

This led to accelerated approval for saquinavir, now dubbed INVIRASE™, by the FDA in November 1995. The drug was licensed at the dose studied in ACTG 229, 600 mg thrice daily, despite the fact that there was already evidence at the time that a dose twice as high was more potent and equally tolerable. Moreover, it was already known at the time that suboptimal doses of protease inhibitors might predispose HIV towards the development of resistance and possibly even cross-resistance to other protease inhibitors.

Thus, ever since saquinavir's licensure at the end of 1995, Roche has known that the licensed dose was suboptimal and that its use could well result in widespread cross-resistance to multiple protease inhibitors.

Had saquinavir rapidly become the drug of choice for people who were failing on nucleoside analogue monotherapy or double therapy, a public health disaster might well have resulted. If cross-resistance became widespread through broad and prolonged use of saquinavir,

many people would not have been able to benefit from the later introduction of more potent protease inhibitors.

Luckily, help was not long in coming. Within three months, both Abbott's NORVIR™ brand ritonavir and Merck's CRIVAN™ brand indinavir were licensed, at doses which were able, when given in combination with new reverse transcriptase inhibitors, to drive viral load beneath the limit of detection in over 75% of patients who could tolerate them for up to one year (Merck 035, etc.), and could prolong health and life when compared with standard of care (Abbott study, ACTG 320). Of note, Roche's survival study used ddC monotherapy, which no one, even then, regarded as standard of care. None of this deterred Roche from charging \$7,000 for a year's supply of INVIRASE, a higher price for a drug weaker than either of its competitors.

Yet Roche faced a quandary. Despite its slipshod, post-haste development plan, two more potent protease inhibitors reached the market within three months of its own accelerated NDA, and even those unversed in the intricacies of retrovirology could tell that they were far more potent. How could Roche redeem its drug?

Two opportunities presented themselves. The first was to use the ability of other protease inhibitors – and particularly ritonavir – to inhibit cytochrome p450 metabolism, thereby increasing the bioavailability, exposure, half-life, and maximum concentration of saquinavir to therapeutic levels. The other, more prosaic, approach was to finally begin addressing the need for a more bioavailable formulation and higher dose of saquinavir itself, unassisted by complex hepatometabolic pathways. Roche proceeded to follow both leads.

As for those participants lucky enough to survive ACTG 229, they were given the chance to enroll in ACTG 333, the first-ever randomized study in protease failures. ACTG 333 randomized 72 SQV-experienced individuals to continue on hard gel cap (HGC) saquinavir at 1.8 grams/day, switch to the more bioavailable soft gel capsule (SGC) formulation at 3.6 grams/day, or switch to indinavir at 2.4 grams/day. They were asked not to switch underlying nucleoside analogues for the first eight weeks of the study. The primary endpoint was virologic response. The study would stop early if no arm achieved greater than a 0.7 log₁₀ reduction in HIV RNA. After an interim analysis conducted when 72 patients reached 8 weeks of follow-up showed that no arm did in fact achieve such a reduction, ACTG 333 was terminated. Participants had received an average of 112 weeks of prior saquinavir therapy. 86% were male, 75% white, non-Hispanic, and the median age was 43. Median baseline HIV RNA was 20,911 copies/mL; 6% had fewer than 200 RNA copies/mL at entry. Median baseline CD4 was 220 cells/mm³. Follow-up for the first 72 subjects was a median 18 weeks (range 12-22 weeks).

ACTG 333: 8 Week RNA + CD4 Results

	<i>HIV RNA (log₁₀) reduction</i>	<i>% undetectable (<200 copies/mL) ever</i>	<i>CD4/mm³ at week 8</i>	<i>CD4 cell change</i>
SQV- HGC	+0.04 log	2/24 (8%)	2/22 (9%)	- 0.4 cells
SQV- SGC	+0.04 log	4/22 (18%)*	2/20 (10%)	+ 37 cells
IDV	-0.58 log	9/21 (43%)	7/19 (37%)	+ 22 cells

* Undetectable at one or more of the week 2, 4, 6, or 8 timepoints.

The study team commented that, "while there was variability in the RNA responses in individual subjects in both the IDV and SQVsgc arms, the mean decreases in RNA and

mean CD4 cell increases in both arms was [sic] less than seen in other trials of protease inhibitor[s] used in combination with nucleosides."

Based on these disappointing results, accrual to ACTG 333 was terminated. Already enrolled patients were allowed to remain on assigned therapy or switched based on virological response. Genotypic resistance analyses are underway. The study will end formally on 14 July 1997 (Bastille Day).

Several things are notable about ACTG 333:

- These were sequential monotherapy patients, many given first AZT, then AZT/ddC or AZT/saquinavir (in ACTG 229), then given SQV-HCG, SQV-HCG or indinavir, without regard to treatment history or virological status at baseline. Certainly the trial would be designed differently if it were begun today [in mid-1997].
- ACTG 333 participants had almost two years (112 weeks) of previous saquinavir experience upon enrolling into 333.
- Most participants switched to SQV-SGC did not experience much of an antiretroviral benefit. The minority who did probably had not been receiving therapeutic doses of SQV-HGC, and hence had not developed SQV resistance.
- Most participants switched to indinavir experienced far less of a viral load reduction than typical with this drug when given as a first protease inhibitor. However, results are given for indinavir patients as a group. Most likely they fall into three subgroups:
 - fully susceptible to indinavir;
 - partially susceptible to indinavir (as suggested by the group average); and
 - wholly resistant to indinavir.

What proportion of patients fall into each category is an intriguing question which may be answered, at least in part, by the ongoing resistance analyses.

After the ACTG 333 fiasco, Roche called various community groups in a series of anxious conference calls to try and squelch doubts raised by the study. Roche's whole marketing campaign for INVIRASE was based on the drug's alleged tolerability and the presumption that you could use it as a first-line protease inhibitor and then go on to use others without fear of cross-resistance. ACTG 333 called this notion into doubt. Moreover, on one of these calls, Roche representatives revealed that saquinavir HGC, when used with AZT and 3TC in antiretroviral-naïve individuals, lowered viral load beneath the limit of detection in fewer than 40% of patients – less than AZT/ddI/nevirapine in INCAS/BI 1046.

Roche's anxieties were deepened when it apparently received a preliminary draft of the DHHS/Kaiser Family Foundation Panel on Clinical Practices for the Treatment of HIV Infection *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* and discovered that – *quelle surprise!* – saquinavir did not make the cut as a strongly recommended first-line protease inhibitor.

Spurred by the prospect of being left off formularies across the country, Roche decided to accelerate its filing for FDA approval of the new saquinavir formulation.

Thus it was that on 14 May 1997 Roche convened a conclave of treatment advocates from the East Coast and the Midwest to hear the exciting new data on its new formulation, soft gel capsule (SGC) saquinavir. The meeting took place at the chic, sleek, postmodern Soho Grand Hotel in lower Manhattan.

They had a new team of eager young investigators and public relations experts who, they earnestly explained, wanted to "open doors", "start an ongoing dialogue" – even "set up a community advisory board". Gasps emanated from the activists who remembered the fiasco of Roche's previous CAB, which resigned en masse amidst screams and spilled shrimp cocktail at a melee at the Times Square Marriot Marquis in summer 1992 over ddC.

Roche's new team, unaware of its predecessors' plight, quickly redubbed the proposed CAB a "task force".

Clinical team manager Laurent Fischer, M.D., presented preliminary data on new (SGC) saquinavir and asserted that SGC provided eight to nine times the exposure of the licensed hard gel capsule (HGC) formulation.

Activists at the meeting were skeptical, assailing Roche's failure to define an MTD before bringing saquinavir to market, and said since the drug company had made its bed, now it must lie in it. Some asked the company to reduce the price of the current formulation by 7/8 (to approximately \$875 per year) to reflect Roche's new assessment of its potency.

Key studies of the soft gel cap saquinavir include NV15107, a dose finding study which "identified 1200 mg three times daily as the preferred dose," NV15182, a safety study, and NV15355C, a virological equivalency study comparing hard to soft gel caps in 160 treatment naive patients in the USA and Canada. They will be randomized to receive (open-label):

- SQV-HGC 600 mg tid + 2 new nucleosides, or
- SQV-SGC 1200 mg tid + 2 new nucleosides

Note that, just to be sure, Roche is giving twice the dose of the new formulation compared with the old (1200 vs. 600 mg tid) – which would likely make it superior even if the new formulation were no more bioavailable (remember Schapiro 1995?). The company claims SGC saquinavir is 12% bioavailable (compared with 4% for hard gel caps), and stated that a monotherapy study among 22 volunteers demonstrated a 1.43 log₁₀ (96.3%) reduction in HIV RNA. The primary "efficacy" comparison in NV15355C will be HIV RNA and CD4 changes over the first 16 weeks, after which SQV-HGC patients will be rolled over to SQV-SGC and followed for a further 32 weeks. The 16 week analysis is due to be complete by summer 1997 and will presumably be the basis for the FDA filing.

Ongoing & Planned Studies of Fortovase™ brand SQV-SGC (May 1997)

	<i>PI + NRTIs</i>	<i>2 PIs/2 NRTIs</i>	<i>PI/NNRTI/NRTI</i>	<i>N</i>
ARV naive	2 studies	2 studies	1 study	437
NRTI-experienced, PI-naive	2 studies	3 studies	2 studies	845
PI experienced	B	2 studies	2 studies	370
N	330	692	630	1,652

Needless to say, several additional studies continue to follow patients on hard-gel cap saquinavir, including the European study in antiretroviral naive patients, SV14604C (AZT vs. AZT/ddC vs. AZT/saquinavir vs. AZT/ddC/saquinavir – though I don't know if this outdated design is still being used).

At the May meeting, Roche had the effrontery to claim that in ACTG 333, "patients switching protease inhibitor showed benefit" and attributed the disappointing results to "evolving treatment strategies".

This evoked considerable outrage. In fact, at the New York meeting and at a subsequent one in California, activists demanded that Roche immediately stop running its "Strategy" advertisements for INVIRASE, and stop advertising the drug as first-line therapy until FDA approves the soft gel caps.

We look forward to seeing whether the FDA concurs with Roche's assessment of the potency of saquinavir HGC, and to its use in creative and novel antiretroviral combinations.

As for those who have believed Roche and taken saquinavir HGC at the approved dose, the company has announced no plans to compensate them for whatever options this therapeutic choice may have foreclosed.

In summary:

- Roche went to market in November 1995 knowing that the dosage and formulation of saquinavir for which it sought approval were suboptimal and might lead to resistance or cross-resistance.
- Roche promoted saquinavir as a first-line protease option for 18 months while studying higher doses and a new formulation.
- ACTG 333 reveals that individuals who took saquinavir HGC are less likely to experience a maximal response from either saquinavir SGC or indinavir.

Individuals considering starting combination therapy with a potent protease inhibitor should avoid starting with saquinavir at least until the new formulation is licensed by FDA, and then only if data support Roche's assertion that it is much more potent than the HGC.

In the interim, the only way to achieve maximal doses of saquinavir (HGC) is to double the dose and take it with a potent cytochrome p450 inhibitor such as ritonavir or nelfinavir. Even among those whose insurers will cover this, it will cost \$14,000 per year for the saquinavir alone (never mind the nukes), which is unconscionable.

Roche should consider some form of compensation for individuals who have taken saquinavir HGC and may have developed cross-resistance to other, more potent protease inhibitors from which they may not now benefit.

After the meeting, Roche invited the activists upstairs for cocktails and "refreshments". Let us hope that the Soho Grand's cocktails were more potent than those being hawked by the unscrupulous pharmaceutical giant. I wouldn't know; I didn't go.

* * *

Treatment Action Group, or TAG, is the first and only AIDS organization dedicated solely to advocating for larger and more efficient research efforts, both public and private, towards finding a cure for AIDS.

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