

The amfAR Treatment Insider

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Introducing the Insider

Welcome to *The amfAR Treatment Insider*, a new publication from the American Foundation for AIDS Research. With each issue of HIVplus, you will receive this extra insert dedicated to digging beneath the hype, the spin and the underlying data to analyze the promise of HIV/AIDS medical research — or lack thereof. Where hope was once the better part of what modern medicine had to offer, we now find a multitude of products and a highly competitive market. But we are only halfway home. Current therapy does not cure the disease, and people with HIV face life-long treatment. Management of long-term side effects and HIV drug resistance have become the issues of the day. Treatment decisions will surely become more convoluted over the next few years.

We expect that treatment will become more straightforward as research progresses, and that is why we are so exasperated by the research gaps exposed in this issue. First, Helen Epstein talks about why there are no available topical agents for stopping transmission of HIV and other STDs. Microbicides of this sort seem a natural concept given the absence of vaccines and condoms' disadvantages. The medical

obstacles to creating microbicides seem relatively simple, yet research proceeds at a snail's pace. In the second part of this issue, we look at a few of the rather long list of anti-HIV drugs that have run into trouble this fall. Here, the rush to market is resulting in slipshod science. Companies ignore critical tests or argue away bad results until forced to face reality. At the same time, we are coming up against the limits of what the body can tolerate as the complexity of treatment regimens grows.

Extended reports on these and other topics are available at amfAR's treatment web site, www.amfar.org/td, which takes advantage of the World Wide Web's capacity for almost limitless information storage and immediate posting of breaking news. If you have internet access, visit our site also for the latest version of amfAR's celebrated *Treatment Directory*, a reference work covering experimental and standard drugs for HIV and AIDS, descriptions of opportunistic infections and lists of other resources. It is now updated on a daily basis.

Microbicides — a Neglected Line of Defense

By Helen Epstein

A diminutive, gray-haired white South African woman in the audience stood up and marched to the podium waving a fist during a recent amfAR symposium on microbicides to prevent sexual transmission of HIV. As she grabbed the microphone from the speaker's hand, the doctors in the auditorium, many with white coats and lab notebooks, were a little startled. "In Natal, where I have just spent the last seven months," she said, "20 to 30% of young women you see today are infected with HIV and [of those who are not yet infected] one in ten will be infected by next year. Really, don't you think we have to change the tempo of microbicide development?" Dr. Zena Stein of Columbia University has reason to be annoyed.

Condoms prevent HIV transmission, but they are still expensive and hard to find in many parts of the world, and people of both sexes often find them uncomfortable to use. These considerations frequently prevent condom use in the U.S., too. In a large American survey of women at risk for HIV infection, only 20% of respondents reported that their partners used condoms, even occasionally.

Women in poor countries are bearing the brunt of HIV as the epidemic continues. The United Nations now estimates that women in sub-Saharan Africa are now 20% to 30% more likely to contract HIV than men. Lacking a vaccine or cure for AIDS, the only hope for controlling the epidemic is a broad-based campaign to promote safer sexual relationships. Women's political empowerment will probably have to be part of such an effort, but this may take generations.

Economics Runs the Science

In the 1980s, AIDS researchers like Dr. Stein realized that a crucial technology for preventing HIV infection would be what have come to be called "microbicides" — creams, gels or suppositories that a woman could discreetly insert into her vagina before sex. Microbicides ideally would kill or block not only HIV but also other sexually transmitted infections. They should be useful rectally as well as vaginally, to protect gay men or heterosexual couples during anal sex.

At the 1992 International AIDS Conference in Amsterdam, Dr. Stein's colleague Sara Back delivered a speech on the need for a good, safe microbicide at a round table sponsored by The Population Council. Her presentation was enthusiastically received. Since then, meetings and official recommendations have piled up, but major financial support has not been forthcoming. Seven years and 34 million cases of HIV later, people are still waiting for what seems like a simple technical advance.

More than 60 candidate microbicides are in the pipeline, but none are expected to be in drugstores very soon. Most of the development of these candidate products is being carried out by small biotechnology companies operating on a shoestring, and by individual academic researchers who are similarly strapped for funds. Both groups depend almost totally on federal grants for testing their products and getting them to the marketplace. The development process costs tens of millions of dollars. Only major pharmaceutical companies are capable of private investments of this magnitude, and they have been squeamish about getting involved in microbicide development.

The large companies worry about liability in case a microbicide turns out to be harmful or unable to protect against HIV infection — or is just alleged to be either. In addition, some potential microbicides also act as contraceptives, and large pharmaceutical companies are generally apprehensive about becoming involved in contraceptive products. The biggest question is how profitable a microbicide might be, especially if the perceived principal market is women with very limited means. Such women are seen as unable to afford microbicides or, for that matter, to use them consistently.

Polly Harrison, director of the Alliance for Microbicide Development, a consortium of researchers and advocates in Silver Spring, Maryland, believes that there is a demand for a good microbicide among middle-class women, too. She points out that several studies, carried out by the European Commission, The Alan Guttmacher Institute and a couple of biotech companies in the Alliance indicate that the U.S. market for vaginal microbicides could be around a billion dollars a year, and the worldwide market at least twice that. Further studies are under way to pin this figure down more precisely and to find out more about potential interest in microbicides among American middle-class and college-age populations.

Ethical Dilemmas

Another obstacle to microbicide development is the matter of staging clinical trials to determine how safe they are and how well they work. Many observers think it will be most efficient to test a microbicide in a developing country, where the incidence of HIV is higher and the costs are lower. Such trials still must meet high ethical standards, just as they would in the United States, and that can be expensive. For example, researchers must provide trial participants with condoms, and counseling about how to use them. It then becomes difficult to determine who is using condoms, who is using the microbicide in question and who is using both.

Providing counseling and testing services to trial participants might be seen as inducement to participate in the trial, especially for an impoverished population, but this too is unethical. Ideally, the entire community, participants and non-participants, would be offered such services, which could become very costly. Researchers must also ensure that the HIV status of participants and non-participants is kept confidential.

Finally, the same question comes up as with any trial product: Shouldn't products that are found to be effective then be made available at affordable — i.e., low - cost to the communities where the trials took place? It isn't clear that any company or organization running a trial would really be willing to do this.

To Wait or Not to Wait

These and other ethical and practical issues complicate the development process and make it unlikely that a microbicide will be on the market for a long time, perhaps five years or more. That's why Dr. Stein is so angry.

At the amfAR conference, she told the audience, "We cannot wait for randomized controlled trials on a large scale... We can't wait even another two years" for a microbicide. Even next year will be too late: Almost half of all young women in Natal may be HIV-positive by then.

Dr. Stein believes that some of the candidate microbicides now in development should be distributed at low cost to women in developing countries now, before further testing. These are products based on compounds that have been used for a long time and are generally regarded as safe. There are also preliminary data to suggest that they work as microbicides, but we

don't know how well they work. Some might reduce the number of HIV infections by 80% while others might reduce the overall risk of becoming infected by 30% or less.

For Dr. Stein, the most critical matter is that the epidemic is already out of control in many countries, and we should be thinking of microbicides as part of a wider safer sex strategy. Developing the perfect microbicide is important, of course, but a "good enough" microbicide could help right now. "This is not just a biochemical problem," she commented in an interview, "if you reckon how many lives could be saved if you just said to women, 'If you can't use condoms, try this. It might work.'"

Besides, a small reduction in the rate of new infections starting now could ultimately prevent more HIV than delaying introduction for the years that fully testing candidate microbicides would take.

A Misstep with N-9

Penelope Hitchcock, Chief of the Sexually Transmitted Diseases Branch of the National Institute of Allergy and Infectious Diseases (NIAID), is sympathetic to Dr. Stein's concerns, but thinks rigorous clinical trials really are necessary, even if they end up delaying women's access to a microbicide.

For thirty years, she says, women have been using a chemical called nonoxynol-9 (N-9), a detergent found in over-the-counter spermicides like Conceptrol. These are formulated to prevent pregnancy, and some people believe that such products might also prevent sexually transmitted diseases. N-9 spermicides kill sperm and HIV in the test tube, and in theory they should kill them in the vagina as well. They also provide a gooey barrier which sperm and microbes cannot penetrate.

Only lately have scientists discovered that nonoxynol-9 is locally toxic. N-9 is a detergent that kills sperm and microbes by dissolving their outer membranes, and it similarly damages the membranes of vagina and cervical cells. The result is inflammation and small cuts called ulcers that may in some cases facilitate HIV transmission. In a recent study carried out among sex workers in Cameroon N-9 products were associated with ulcers in the vagina and vulva and provided no additional protection against HIV infection when used with condoms.

"I actually think the tragedy here is that we are 20 years into the epidemic and doing experiments which we

should have done a long time ago, frankly,” Dr. Hitchcock said. “[T]he idea that women would put these products in their vaginas and cause lesions and no one would seem to think that’s important troubles me greatly... When people say yes [to a particular episode of sexual intercourse] because they believe a product can prevent infection or protect them, and there’s no evidence for that, we have harmed them, especially if they have taken a risk that they would otherwise walk away from.”

Newer Alternatives

At present, researchers are studying a number of other products that work in much the same way as N-9 yet might be less irritating. Some, like C31G and Triton-X 100, have already proven less toxic than nonoxynol-9. N-9 itself can be made safer by putting it in a gel or by reducing the concentration of the chemical used. Advantage S (formerly Advantage 24), a bioadhesive gel that sticks to the mucosal lining of the vagina and contains a low dose of N-9, is in clinical trials at the moment and seems much safer than many other nonoxynol-9 products.

It remains that these detergents’ mechanism of action has broad toxic effects, and many may ultimately prove unusable. And, of course, they also kill sperm, which would make such products undesirable for women who wanted to become pregnant but still needed to protect themselves from infection.

For this reason, John Moore of the Aaron Diamond AIDS Research Center thinks that researchers must take a more scientific, rational approach to microbicide design. The ideal microbicide would be based on a small molecule that specifically blocks part of HIV’s lifecycle while leaving human cells alone. The best microbicides might be ones that jam up the entry mechanism by which the virus’ envelope merges with cell membranes. A successful microbicide should also be quickly and cheaply synthesizable and stable enough for long-term storage.

“This is the kind of issue that the researchers developing microbicides now really need to discuss with the scientists at pharmaceutical companies,” he said in an interview. “The NIH and the small biotech companies are desperate to do something, but at the moment they are mainly taking things off the shelf,” and not using rational design. “They need to sit down with some of the scientists at companies like Merck or Glaxo and ask

them, ‘Would you consider scaling this up? Is this practical?’”

The U.S. government last year spent only about \$23 million on microbicide research, an infinitesimal part of the \$1.8 billion the government spent on all AIDS research, notes Polly Harrison. She and other advocates are fighting hard to persuade officials to increase funding for the year 2000 and beyond, but it’s an uphill struggle. Surveys conducted in the U.S. and in developing countries strongly suggest that women and men would welcome microbicides and would be willing to participate in large-scale trials. For now, it all depends on when the pharmaceutical companies and the federal government are willing to provide the investment necessary to make that happen.

There are a few glimmers of industry interest. Several big pharmaceutical companies, including Merck and Schering-Plough, are considering adapting some of their experimental HIV drugs for use as microbicides. The companies refuse to comment on these efforts, but these agents might be harmless if applied topically in the vagina or rectum even if they have side effects if taken by mouth. The research community may hear more about these products in the months to come, but the women in Natal will still be waiting.

Gilead Puts Adefovir Out of Its Misery

By Dave Gilden

At the close of business on Friday, December 3, Gilead Sciences announced that it was canceling future HIV-related work on its compound adefovir. Gilead is terminating or phasing out all adefovir clinical trials, rolling over participants to the expanded access program. This latter program, which at present provides adefovir to about 4,000 persons, will otherwise accept no new applicants after Friday, December 10. Since the average time that patients take part in the expanded access program is only about nine months, adefovir will soon disappear from the HIV arena. Research is continuing on its use in hepatitis B, however.

Adefovir has been under development for more than a decade. It was the subject of a negative vote by the FDA’s Antiviral Advisory Committee on November 1.

This panel of independent consultants concluded that there was not enough evidence to warrant adefovir's accelerated approval (see earlier article on this website). Adefovir's slow march to the market was marred by great shifts in treating HIV. The new highly active therapies make adefovir, with its modest activity and large toxicities, seem a throwback to a gloomier period in HIV care.

Gilead was never able to reorganize its program to prove that adefovir had a crucial role to play in the new environment. For example, the NIH-sponsored Community Program for Community Research on AIDS (CPCRA) embarked on a 2,200-person trial, designated CPCRA 039, to test adefovir against both CMV and HIV by adding it or placebo to anti-HIV combinations prescribed to people with AIDS. Adefovir's broad-spectrum antiviral activity could be an important advantage, if it could be confirmed. Unfortunately, the CPCRA trial started just as protease inhibitor combination therapy came on the scene, when approved drugs were suddenly successful at suppressing HIV and stabilizing patients. CPCRA 039 lagged because of slow enrollment and finally fell apart. Disease progression was now too slow to detect any benefit from adefovir, nor did the viral load results reveal any effect of the drug over and above that obtained with the potent new regimens.

Gilead never replaced CPCRA 039 with a large trial designed to document adefovir's supposed advantages, mainly its availability as a rescue agent in patients whose HIV has evolved resistance to most other drugs. Instead, the few small trials that took place in the last several years only raised further questions about adefovir's activity and interactions with other drugs. The worst blow was the finding that long-term use of adefovir carried with it a high probability of kidney malfunction that would force the drug's discontinuation.

Rather than investigate ways to prevent this build-up, Gilead merely cut the adefovir dose by half. It then insisted against all skepticism that the reduced dose was both safe and effective. Gilead launched only one real trial to prove out this dose, and its 20-week results left the FDA bemused. The data could easily be interpreted as showing no activity at all. And long-term safety data for the reduced dose was almost completely lacking. In the end, the FDA insisted on waiting for the outcome of current trials before reconsidering marketing approval.

It would have taken another 18 months to collect these results, and meanwhile the expanded access

program would have to continue. Gilead refused to bear the time and expense, especially since it will have tenofovir, adefovir's apparently safer and more active sibling, ready for approval by then. (But note that for tenofovir, too, long-term data are lacking so far.)

Carol Brosgart, M.D., Gilead's Director of Clinical Research for adefovir, said in an interview, "Everything got delayed with adefovir, and it became a very complicated application package. We're being realistic and diverting resources onto our other product. Tenofovir will take most of adefovir's sales when it comes on the market."

Tenofovir ironically is just as old a compound as adefovir, and many observers wonder why the company didn't make this move a long time ago. Marty Delaney, founding director of Project Inform in San Francisco, observed, "As far as I'm concerned, Gilead has finally done the right thing, ending years of research that wasted the time and sometimes the health of our most precious resource: HIV-positive people willing to risk their own health as study subjects in pursuit of better therapy."

ddI Plus Hydroxyurea: Watch Out for Your Pancreas

By Dave Gilden

ddI is one of the most potent nucleoside analogs prescribed for HIV, but it does have considerable drawbacks. Most notably, it attacks the pancreas, the organ that produces critical enzymes for digestion of fats in the small intestine. Damaged pancreatic cells can leak digestive enzymes into surrounding tissue, causing their breakdown.

Acute ddI-induced pancreatitis is a very painful, life-threatening condition. Pancreatitis occurred in up to 7% of trial participants with advanced disease receiving ddI monotherapy. This was a rate two to three times that of those receiving AZT monotherapy in the same trials. Pancreatitis associated with ddI occurred very rarely in trials enrolling volunteers at earlier stages of HIV infection.

This year, pancreatitis cropped up in an unlikely population: a cohort of persons whose successful

antiviral treatment had nearly normalized their CD4 count while reducing their HIV to undetectable levels. The cohort consisted of participants in ACTG trial 5025.

Pancreatitis Deaths Shut Down ACTG 5025

ACTG 5025 had a curious history, and its untimely conclusion was more curious still. The trial was studying whether adding hydroxyurea to a standard drug combination would increase the likelihood of long-term viral suppression. Hydroxyurea, a cancer chemotherapy, reduces cell activation and thereby lessens the opportunity for latent HIV hidden in cells to spring to life as the cells proliferate. It also enhances ddI's anti-HIV effect, making this nucleoside analog active even against HIV that has mutated to resist it.

(This enhancing effect stems from hydroxyurea's inhibition of an enzyme that produces the natural functional nucleoside (deoxyadenosine) replaced by ddI's intracellular end product. The resulting deoxyadenosine scarcity increases the likelihood that HIV's reverse transcriptase will accept the ddI end product instead. The result is a fatal break in the DNA gene chain spun out by reverse transcriptase as HIV attempts to infect new cells.)

ACTG 5025 was a highly ambitious effort to characterize hydroxyurea's benefits once and for all. It sought to leap from small uncontrolled studies to a 400-person randomized trial of standard triple therapies with or without hydroxyurea. Enrollees had to have had minimal viral loads (below 200 copies/ml) while on a combination of AZT, 3TC and indinavir. They were divided to an arm receiving ddI/d4T/indinavir/hydroxyurea or two comparison regimens — either d4T/ddI/indinavir minus the hydroxyurea or the original AZT/3TC/indinavir combination. In the end, ACTG 5025 interested few people who met its entry criteria. The trial did find 202 persons, most rolled over from the ill-fated ACTG 343. Nearly all recruits had viral loads below 50, the ultrasensitive viral load test's limit. Their average CD4 count was 617, which is at the low end of the normal range.

ACTG 343 represented an attempt to simplify therapy — by putting untreated patients on AZT/3TC/indinavir for six months and then trying to reduce their regimen to either AZT/3TC or just indinavir. These two maintenance therapies failed miserably as people with previously suppressed HIV

began experiencing viral rebound. The University of California San Diego researchers running the trial terminated it early. They put everyone back on the original regimen, and viral loads returned to very low levels. The investigators then moved on to ACTG 5025, which, with the benefit of hindsight, seems like another imprudent maneuver with still more undesirable results.

Two people receiving hydroxyurea in ACTG 5025 died of pancreatitis. This is a particularly tragic outcome since these volunteers were doing fine on their previous therapy. Presumably, they would not have died if they had not entered this trial.

All told, 13 persons on hydroxyurea dropped out because of ddI-associated toxicities (mostly related to pancreas, liver and nervous system damage). Only two had to stop their long-time AZT/3TC/indinavir combination, while four discontinued ddI/d4T/indinavir (two because of nonfatal pancreatitis). To make matters worse, there was also a trend toward increased HIV rebound in the trial's hydroxyurea arm.

Not only was ACTG 5025 halted, but the recently commenced ACTG 5039 was also canceled because it included the ddI/d4T/hydroxyurea combination. (ACTG 5039 was attempting to test this combination as a simplified maintenance regimen after successful protease inhibitor combination therapy.)

What went wrong? ACTG 5025 co-chair Douglas Richman, M.D., says, "The most likely explanation is that hydroxyurea potentiates ddI's toxicities on the pancreas and liver as well as its antiviral activity on HIV."

(Pancreatitis can be a sign of dysfunction in the mitochondria, the energy-producing bodies in the cells that carry their own genes within them. It is not particularly surprising that hydroxyurea would enhance ddI's effect on mitochondria in the same way it does on the virus because, unlike the main gene set in the cell nucleus, both have gene replication mechanisms that cannot correct for ddI's disruptive effects.)

Dr. Franco Lori, of the RIGHT Institute in Georgetown, D.C. and Pavia, Italy, has been one of the pioneers of hydroxyurea use. He still defends the compound. "When I heard about 5025," he says, "I reviewed all the recent trials, involving some 500 people in all, some on ddI, d4T and hydroxyurea, some on ddI and hydroxyurea. There was not a single hint of pancreas or liver problems." But all these studies were small, did not contain potent regimens by today's standards or lacked an appropriate triple combination control arm.

The FDA Takes Bristol to Task

In the meantime, Bristol-Myers Squibb, the manufacturer of hydroxyurea as well as ddI and d4T, was getting into trouble with the FDA. Although hydroxyurea is still highly experimental, the company was sponsoring seminars about hydroxyurea's efficacy and safety as an adjunct to ddI-containing regimens. On October 28, the FDA sent Bristol an official "warning letter" complaining about such representations, particularly a lecture given four days after the ACTG 5025 termination notice went out.

Under the FDA's prodding, Bristol greatly reinforced the warnings on the ddI package insert. It also sent a notification to health care providers on November 11. The providers letter described the two deaths in ACTG 5025 as well as two pancreatitis-related deaths in two separate company trials. All four of the deceased were taking ddI plus d4T, but only the 5025 volunteers were also getting hydroxyurea. The four were on protease inhibitors, too, nelfinavir in one case and indinavir in the other three, and they had very low viral loads and near normal CD4 counts. Three had additional risk factors for pancreatitis — obesity, high blood triglycerides (due to a familial predisposition), or gallstones. (Prior pancreatitis, which sometimes occurs in people with AIDS due to infections, is an extremely serious risk factor. Other risk factors include alcoholism, and concomitant use of certain drugs, including pentamidine for pneumocystis pneumonia.)

Bristol's warning letter added an extra risk factor: combining ddI with d4T, "with or without hydroxyurea." Most of the recorded deaths due to ddI-related pancreatitis since 1998 have been in individuals taking d4T in addition to ddI, some with and some without hydroxyurea. Until now, there has been no indication that d4T causes pancreatitis, but it does sometimes impair liver function and may increase blood lipids in some people. These two effects could contribute to pancreas damage, but it is hard to determine d4T's role because at this point, nearly everyone who takes ddI also takes d4T.

Monitoring for Pancreatitis

The ACTG 5025 team is now attempting to track down all the factors that added to the hydroxyurea arm's problems. One thing is already clear: Monitoring for pancreatitis was not taken seriously enough. The

symptoms in the two persons who died were first attributed to other causes, and in one case, a clinic not associated with the trial kept the patient on ddI. Symptoms such as sharp abdominal pain, nausea and vomiting as well as elevated blood levels of pancreatic enzymes should lead to suspicion of pancreatitis and prompt cessation of ddI and hydroxyurea. ACTG 5025 did check study participants every eight weeks for high blood levels of amylase, one enzyme produced in the pancreas. Pancreatitis can arise suddenly, though. Also, amylase is produced by salivary glands, too, and may not be a specific enough indicator. Checking the levels of lipase, another pancreatic enzyme, is preferable.

According to Bristol researcher Colin McLaren, "Pancreatitis has not been seen much for a while. Doctors need to be aware that it is still a possibility. When people come in with nausea or abdominal pain, don't think that it is just gastroenteritis. Investigate pancreatitis, and discontinue ddI."

Saving Face When a Drug Goes Bad

By Dave Gilden

Last September, at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Triangle Pharmaceuticals enthusiastically reported the results from an initial trial of its new drug, emivirine. But emivirine's fortunes suddenly took a turn for the worse a week after the conference closed, and the drug increasingly seemed headed for limbo as the fall progressed.

Emivirine (brand name: Coactinon) is a nonnucleoside reverse transcriptase inhibitor (NNRTI) that Triangle, a feisty biotech startup, had hoped would compete successfully with DuPont's efavirenz (Sustiva) and Roxane's nevirapine (Viramune). The trial described at ICAAC tested two different doses of emivirine together with the two nucleoside analogs ddI and d4T, a dual combination that is now raising safety questions (see article on ddI). The trial recruited 196 persons with little to no previous treatment. Half of them achieved viral loads less than 50 copies/mL by week 24. These results, if not extraordinary, were at least respectable and kept Triangle's stock near its 1999 high point.

Triangle's stock crashed on October 7 when the

company announced that another emivirine trial, MKC-303, had failed miserably. Triangle considered this 275-person trial central to its attempts to gain FDA approval for the drug. This study matched a standard combination of two nucleoside analogs and the protease inhibitor nelfinavir to a four-drug combo that added emivirine to the other three drugs. It turned out that emivirine so sped up activity of liver enzymes (designated as CYP 3A4) that they quickly eliminated most of the nelfinavir in the blood. Emivirine had a similar effect on indinavir and probably the other approved protease inhibitors.

“The overall findings indicate that Coactinon is most likely to be useful as initial therapy in protease-sparing regimens,” said David Barry, Triangle’s chief, trying to put the best face on the situation. The company’s own tests indicate that emivirine will accelerate the breakdown of any of the multitude of medications metabolized by CYP 3A4, greatly reducing their effectiveness.

Nevirapine and efavirenz have the same problem, but to a lesser extent, and Triangle has been slow to admit that emivirine presents a special challenge to doctors treating patients with HIV and related conditions. Eighteen months ago, at the 12th World AIDS Conference, Triangle reported that emivirine increased nelfinavir clearance by a modest 30%. This figure was obtained using emivirine at 100 mg twice daily for a week in combination with nelfinavir. Triangle has since chosen 750 mg as the best dose for emivirine. Triangle raised the usual nelfinavir dose by a third for MKC-303, but this could hardly make up for the extra liver activity induced by 750 mg of emivirine.

Blaming the Messenger

In early December, Triangle announced that the FDA said it needed to perform more studies if

emivirine was to have a chance at receiving marketing approval. Although Triangle had just lost a major trial in MKC-303, the company complained that the agency was unreasonably tightening its rules for drug approval. It stated it would devote no new resources to emivirine pending the results of current trials.

MKC-401 has become the critical ongoing trial. This trial tests emivirine plus d4T and Triangle’s experimental nucleoside analog FTC, again in persons with no prior therapy. The control arm will receive a triple nucleoside analog combination of abacavir/d4T/FTC.

Triangle says that the FDA objected to MKC-401 because triple nucleoside combinations, like the one in the control arm, are not considered a preferred initial regimen. This trial is perplexing for a number of additional reasons. MKC-401 is comparing emivirine head-to-head against abacavir. These agents are not in the same drug class and would not ordinarily substitute for each other. Also, both arms of the trial will receive a second experimental drug, FTC, making it hard to isolate emivirine’s activity.

“We told Triangle time and again in community meetings that they should test emivirine against efavirenz, not abacavir, in 401,” said Ben Cheng, Assistant Director of Information and Advocacy at the San Francisco-based Project Inform.

Triangle would have avoided much of its difficulty with the FDA if it had listened to the community activists. But the FDA’s attitude may not really matter. It would at this point take very exciting trial results to out-balance emivirine drawbacks, and most observers think that Triangle will drop the compound completely when it finds an opportune moment.

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