Conflicts in Pharmaland

It takes a lot to be an informed consumer in the age of combination therapy. Frank Pizzoli asks what we don't know about the drugs we take -- and why.

April 1, 2001 By Frank Pizzoli

Call it a Sustiva dream. The dozens of big pharmaceutical and little biotechnology companies in the AIDS research game have merged and remerged until there are only three behemoths left. Each sends a board member to Larry King Live to announce studies of a dozen new HIV drug combinations. "Let the chips fall where they may on profits," they say. "Science will lead the way." Cut to the peaceful night sky of an Alluna commercial.

Then you wake up, wet...but from side effects.

It would be nice to rise each morning safe in the feeling that research was moving steadily ahead, toward better HIV drugs, a vaccine and a cure. After all, the U.S. system, with its hybrid of government-funded basic science research and pharmaceutical-funded drug development, has produced almost all of the drugs in our AIDS medicine cabinet. But as Larry Kramer's WAKE UP wheatpastes urban centers with a technicolor list of antiretroviral toxicities, and the feds issue new recommendations to hold off on HAART for as long as possible, questions about the current state of AIDS research have reached critical mass. Is our system truly set up to speed the development of drugs that heal the immune system or target HIV in new ways? Is it even primed to produce the data we need on toxicity, dosage and treatment strategy for the meds already on drugstore shelves? Or do the pressures of the marketplace limit our ability to get lifesaving information and drugs?

HIVers' needs are deceptively simple. "Before a drug is approved," says Gregg Gonsalves, director of treatment advocacy at New York City's Gay Men's Health Crisis, "we want to know more about how it works in combination with competitors' drugs and in comparison with other drugs in its class. After marketing, we want comparative information about side effects. And, of course, we need new drugs."

The hard part is getting there. "Activists must focus on a drug company's inner layers, where research and development decisions are made, sometimes based on science, but sometimes based on marketing," says one big-pharma insider, who has worked on HIV product teams for two different drug-makers and who, fearing repercussions, requested anonymity. "It's different than the old days when activists said, 'Make a drug, any drug,' then fought price wars," he says. "R&D

has moved from simple arithmetic to calculus."

"Today's Competitor Is Tomorrow's Collaborator"

Drug development is a famously high-stakes enterprise. Only one in 10 compounds in phase III human efficacy trials gets Food and Drug Administration (FDA) approval; only one in three of these ever turns a profit; and pharmaceuticals depend on 20 percent of these winners to create 70 percent of their profits. These odds encourage drug companies to avoid research long shots and any data that might be damaging to their meds already on the market.

Mike Barr, editor of the treatment newsletter TAGline, sat from 1990 to 1994 on the HIV Research Agenda Committee, which proposed protocols for the federal AIDS Clinical Trials Groups (ACTG), set up to answer what Barr calls "practical public health questions" about HIV treatment, including comparative studies of drugs in the same class. He watched as the ACTG bowed to pressure from drug companies, which refused to supply meds for studies over which they had no control. Barr says this legacy has become extremely costly in the age of HAART: "After the early protease euphoria, people really wanted head-to-head studies, comparing popular drugs such as Crixivan and Viracept in terms of efficacy, viral breakthrough and toxicity. But it was just impossible to make these trials happen through the ACTG."

Robert Schooley, MD, the current chair of the Adult ACTG, finds Barr's characterization a bit harsh. "We work with the drug companies as collaborators," he says, "and part of the quid pro quo is the provision of drugs. When we've been unable to scientifically agree, we have purchased drugs and done the study without their involvement. But we can only do so sparingly, due to our very limited budget." He mentions two current protocols that pit drugs of the same class against one another -- one comparing nucleoside combos, the other comparing protease regimens -- but adds, "Not all of our studies should be drug A-vs.-drug B designs."

Merger mania -- whether big fish swallowing small biotechs, or big fish schooling up -- has heightened the risk of drug hoarding. The 84 AIDS meds on the market (counting only the 15 distinct antiretrovirals and the 69 meds for opportunistic infections covered by New York's AIDS Drug Assistance Program) are made by more than 40 firms, with most marketing only one AIDS product. But four megacompanies have surfaced as AIDS heavyweights, with more than a third of AIDS meds among them: Roche (with two antiretrovirals and seven OI meds), Bristol-Myers Squibb (two antiretrovirals and four OI meds); Pharmacia & Upjohn (one antiretroviral and five OI meds) and, in the lead, GlaxoSmithKline (GSK), created by Glaxo Wellcome's $73 billion December merger with competitor Smith Kline, with four OI meds and four antiretrovirals -- AZT, 3TC, abacavir (Ziagen) and amprenavir (Agenerase) -- more than one quarter of all antiretrovirals on the market. These giants have shown a preference for studying their own in-house combinations, rather than combos that involve competitors' popular drugs. Agouron, for example, a Pfizer subsidiary, is now testing its promising non-nuke, capravirine, only in combination with its own protease, nelfinavir (Viracept).

This tendency not to share shows up in other ways. GSK's recent contributions to the HIV drug arsenal have been limited to tweaking its own already-approved products to make them more

adherence-friendly, marketing Combivir (AZT plus 3TC) and Trizivir (AZT, 3TC, abacavir) as single pills. The company is now aiming for a third retread: 3TC is in phase III trials for once-daily dosing. Roche is likewise studying once-daily dosing of saquinavir (Fortovase), and several other firms are looking at simplified dosing of their current antiretrovirals.

Amy Keller, GSK's international team leader for Trizivir, says, "Let me assure readers that each of the compounds will continue to be made available for use with other combinations of drugs not made by GSK."

But many advocates say companies need to pay more than lip service to support intercompany trials. "It's not OK that the companies put roadblocks up for comparative trials of drugs from two or three different companies," says Gonsalves. "They need to supply their drugs to the networks [such as the ACTG] who want to test them -- for free."

AZT co-inventor David Barry, MD, chairs the InterCompany Collaboration for AIDS Drug Development (ICC), a consortium of researchers from 15 AIDS drug-makers. The group was formed in 1993, with Merck's help, to spur the comparative studies pharmaceuticals fail to fund on their own. So far, according to Barry, the ICC -- which he says includes "no marketers, only scientists" -- has sponsored six to eight studies, including some of the first studies of combo therapy, and another 50 pharma-funded trials have sprung from networking at ICC meetings. "The reality," Barry says, "is that people with HIV use these drugs in combinations, and drug resistance is our common enemy. Like it or not, today's competitor is tomorrow's collaborator."

Despite Barry's upbeat rhetoric, GMHC's Gonsalves says that the ICC has yielded little useful data. "They've been around for years," he says, "and what do they have to show? What we really need is a collaboration that's more than PR." The anonymous pharma insider says that far from backing studies that give PWAs the information to make the best treatment decisions, drug companies in the ICC fight for the highest possible dosage of their drug in cross-company studies. (Barry denies this.) Given the association between dosage, toxicity and resistance, says the insider, "Any study ought to be looking for the smallest amount of a compound that is effective."

"Drug Companies Are Not Going to Bridge the Gap"

Michael Joyner, GSK's manager of health care coalitions, says that the presence of pharmaceutical giants will encourage, rather than repress, effective new HIV research: "With mergers we'll see the formation of new, competing companies organized by individuals who do not survive reorganization."

This Pollyanna perspective may be half right. Barry was one such nonsurvivor, starting up Triangle Pharmaceuticals after a hostile Glaxo takeover of Burroughs Wellcome, where he'd been president of research labs. Triangle currently has three nukes, a non-nuke and a protease in development -- more new HIV drugs, farther along, than most larger pharmaceuticals. As for research into whole new classes of drugs, Merck and other heavyweights do have several potential integrase inhibitors in the pipeline, but much of the promising entry inhibitor research is going on at small biotechs, such as Progenic, Advanced ImmuniT and Trimeris.

“Many large firms, such as Merck and GSK, have extensive research programs in new classes of drugs,” says Martin Delaney, founding director of the San Francisco-based Project Inform. “Big companies can pick a few targets and go after them intensely. Small companies can’t compete with that.” But Delaney points to fruitful collaborations between the big guns and bantam weights like Trimeris, the small company that developed T-20, likely to be the first fusion inhibitor to market. Too poor to pay for the high-tech manufacture of large quantities of the compound, Trimeris collaborated with deep-pocketed Roche to push the drug to phase III trials and prepare for market-scale production. Likewise, GSK’s amprenavir was discovered by Vertex, a small, innovative biotech, which then partnered with GSK for clinical development, production and marketing of the drug. And Triangle has formed a similar partnership with Abbott.

To Gonsalves, the prominent role of these cash-poor biotechs in AIDS R&D points to how little novel drug development is going on. While the National Institutes of Health (NIH) funds basic science, he says, no one’s there to translate breakthroughs into potential treatments that could pique pharmaceutical interest. “Drug companies are not going to bridge this gap on their own,” he says. “We need the NIH to work with industry to boost their efforts on developing drugs don’t attack the same old viral targets. While the development of entry inhibitors is a good start, there are other viral genes and proteins ripe for exploitation.”

“The FDA Has Little Power to Compel Long-Term Studies”

Even as advocates call for investment in ambitious new research, they’ve raised concerns about the long-term effects of fast-tracked drugs already on the market. Fast tracking, an activist demand formulated in the treatment-hungry late ’80s, has allowed lifesaving meds to hit the market with 24-week, rather than the usual 48-week, phase III data. Whenever the FDA grants a drug approval, the agency requires longer term post-marketing (phase IV) studies, especially important with fast-tracked meds. There’s just one problem, says GMHC’s Gonsalves: “The FDA has little power to compel companies to perform these long-term studies. For most AIDS meds we still only have pretty short-term data.”

In effect, post-marketing studies depend on the kindness of pharmaceuticals. But because such studies could either expose toxicities that did not show up in short-term trials or reveal that a drug’s benefits are not sustained over time, the profit incentive works against PWAs’ need to know. The Ralph Nader group Public Citizen released a report in April 2000 documenting the near-total lack of phase IV data. Out of 88 drugs approved by the FDA between 1990 and 1994 with phase IV requirements, only 11 of those studies were completed as of December 1999. Out of 107 drugs approved between 1995 and 1999, no phase IV studies had been completed.

Some drug companies have done the right thing on their own. Merck, for example, completed food-intake studies in 1997 for its protease, indinavir (Crixivan) -- information that helps HIVers on the drug to promote absorption and minimize toxicity. But many other companies have not. Even as anecdotal data mounted that saquinavir was elevating PWAs’ triglycerides, maker Roche continued to recommend that the drug be taken with “high-fat foods” to aid absorption. Pressured by activists to conduct food-intake studies that would help saquinavir-takers minimize risks, Roche refused. “Marketers feared a bad rap in the media,” says the pharma insider. Last year, a study in

Holland finally resulted in new recommendations that may help limit triglyceride elevation: The drug, Roche now says, should be taken with a light meal.

The cost of this catch-as-catch-can data collection became tragically clear recently in the cases of nevirapine (Viramune), ddI and d4T. Though pre-marketing safety data from Boehringer Ingelheim/Roxane (BI) found that nevirapine caused a strong hypersensitivity reaction -- including skin rash and liver failure -- in a miniscule fraction of those who took it, increased reports of severe reactions prompted the FDA to ask BI to alert physicians (see “Two Strikes,”); BI has since updated the drug’s package insert. Similarly, following the deaths of three pregnant women taking ddI and d4T, Bristol-Myers Squibb sent letters to doctors warning that the nukes should be used with caution by expecting mothers.

“We need to pressure the FDA to enforce post-marketing studies,” says Phil Goropoulos, president of central Pennsylvania’s AIDS Community Alliance. “In the rush to develop treatments, we put efficacious ahead of safe. That trend must be reversed.” The only tool the FDA has to enforce phase IV is the threat of pulling a drug off the market, an unpopular move with both producers and consumers. Gonsalves says the agency needs a better carrot and stick, such as the power of the patent: extending it on drugs with the required phase IV data, or shortening it on drugs without.

“I’ve Heard of Payments of $6,000 per Patient”

In “The Kept University,” in the March 2000 Atlantic Monthly, Eyal Press and Jennifer Washburn explored another worrying trend in drug research: More and more studies outside drug-company walls are nevertheless sponsored, and tightly controlled, by the firms themselves. Press and Washburn wrote that “commercially sponsored research is putting at risk the paramount value of higher education -- disinterested inquiry.” According to former New England Journal of Medicine editor-in-chief Marcia Angell, MD, the pressures are only intensifying. “Biotechs hoping to be snatched up often push marketing themselves to potential buyers over science,” she says. “Academic centers are hurting under lower reimbursements from Medicare, Medicaid and managed care. So they’re more willing to be jerked around by drug companies.”

“This is not a hidden evil,” says Joseph Sonnabend, MD, clinic physician at New York City’s St. Luke’s-Roosevelt Hospital Center and the director from 1991 to 1996 of the Community Research Initiative on AIDS, a drug trial network. “We’ve known about it for a long time. I’ve heard of payments ranging from $2,000 to $6,000 per patient going to private-practice doctors who enroll their patients in drug company-sponsored clinical trails. But no one can cast the first stone, so many are guilty of the same behavior.”

TAGline editor Barr witnessed this dynamic firsthand when he worked as a clinical research associate at St. Vincent’s Hospital in New York City, where, he says, payments to docs reached $8,000 per patient completing a protocol. “At one point, we needed around $60,000 to help pay for staff, computers and other overhead, so we brainstormed a whole series of studies, one for each drug company, for which we might be able to get their support,” Barr says. “Sadly, research agendas are set this way more and more.”

Once a study like this gets funded, he says, “you’re completely beholden to the sponsor.” He mentions one that he helped coordinate, looking at a dual-protease combo of Crixivan, ritonavir (Norvir) and Sustiva (efavirenz) as a strategy for HIVers experiencing viral resistance with one-PI combos. “The Norvir dose we had chosen, based on the most recent data, was 200 milligrams,” Barr recalls. “Abbott was aghast and said they would not fund the study unless we used their suggested dose of 400 mg. They didn’t want any more data that would encourage using less of their drug than was currently the standard practice. Practical folks that we were, we said, ’Fine. Just give us the money.’”

“Fortunately,” Barr adds, “patients were wise enough not to sign up, so the study closed due to poor enrollment.” (Abbott spokesperson Cindy Resman says that “no one knows the appropriate dose,” but that since Sustiva, a non-nuke, lowers levels of other proteases, Abbott “felt more comfortable with the 400 mg dose.”)

For Sonnabend, the critical question is: Who’s looking out for patients pressured into joining trials of risky regimens? “We need to push government agencies to do their job in protecting the public safety,” he says. Though every trial has to be vetted by the participating clinic’s Institutional Review Board, Barr says that “there is often not the expertise on these panels to catch badly designed protocols.”

Effective review at the tail end of drug approval is equally scarce. A USA Today study of FDA advisory committee meetings from January 1998 to June 2000 showed that 54 percent of the time, researchers on these panels -- who recommend for or against drug approval -- had a direct financial interest in the drug they were asked to evaluate. While federal law prohibits the FDA from using experts with such conflicts, the agency waived the restriction more than 800 times during this period.

Most medical journals have shown themselves unable to police study data, either. After then editor-in-chief Angell launched a full-scale investigation into conflicts of interest at the NEJM last year, she wrote, “There is now considerable evidence that researchers with ties to drug companies are indeed more likely to report results that are favorable to the products of those companies than researchers without such ties.”

“Companies That Break Ranks Will Clean Up”

Effective treatment of HIV requires informed choice -- and that means a research structure that can meet PWAs’ needs. According to pharma researcher and ICC chair Barry, “[The system] is working more than it isn’t,” and Project Inform’s Delaney agrees. “Despite its downsides, the profit motive works pretty well when it comes to drug development,” he says. “Any company that breaks ranks and offers something better will clean its clocks in the marketplace.” But Delaney, along with many leading AIDS researchers and advocates, allows that the system could benefit from a major tune-up.

Delaney applauds an overdue FDA decision to encourage the study of salvage therapy: The agency has begun to work with researchers to design new protocols and has pledged to accept

data from studies that contain multiple experimental drugs.

AIDS researcher Steven Miles, MD, associate professor of medicine at the University of California at Los Angeles, would like to see the FDA go further, by halting fast-track for nuke, non-nuke and protease knockoffs. “That would definitely make everyone -- industry, activists, doctors, government -- stop and think,” he says. “To say, ’We’re not giving you early licensure unless you show us how this drug is better than what’s already out there.’”

GMHC’s Gonsalves calls for a massive “public/private partnership” to bridge the gap between basic science and big-pharma drug development.

Any of these tactics could spur pharmaceuticals to engage in more ambitious new drug development. Each also hints at the need for a new age of AIDS activism. Advocacy may work better than Alluna for easing the late-night anxieties of HIVers who, burning through their remaining treatment options, rush to the medicine cabinet for new drugs and find it bare.

PORTRAITS IN GREEN; 6 AIDS INC. PLAYERS

Sharon Stone: Chair, Campaign for AIDS Research, American Foundation for AIDS Research, Beverly Hills

She may not be an AIDS queen like Elizabeth Taylor or Elton John, but Sharon Stone holds her own as the reigning princess of the AIDS benefit circuit. Since 1995, when the model-turned-actress joined amfAR as its celebrity spokeswoman, the once-financially troubled group has gone from red ribbons to black tie. “I raise the funds that pay for AIDS research,” explained Stone, 42, during a New York City gala last December that netted more than $2 million. That put the total she helped raise in the year 2000 at more than $3.5 million, including $500,000 at the Venice Film Festival and $1 million at a Dallas auction.

Despite rumors, Stone’s appearances are all pro bono, not to mention a few perks that most private donors are all too happy to pay for (an anonymously donated private jet to a Cannes event, for instance). The Oscar-nominated actress often recalls the death of her acting coach and close friend, Roy London, who died of AIDS in 1993, as a turning point that led to her involvement. “I would like to see a world where generations of people will not perish and die senselessly,” she tells POZ in her sincerest straight-from-the-script voice. Asked to sum up her duties as an AIDS moneymaker, Stone, faced with a double-digit drop in donations industrywide gruffly replies: “Challenging.”

Ina Goldberg: Medical Liaison, DuPont Pharmaceuticals, Middletown, New Jersey

Medical liaisons walk a fuzzy line between drug marketing and scientific education. But Ina Goldberg, who works on Dupont’s Sustiva (efavirenz) campaign, says that she’s clear about her

role. “My job is to provide health care professionals with the latest science in a timely and unbiased way,” she says. “I don’t sell and I don’t promote.” Instead she regularly meets with New York City doctors to update them about data from post-approval trials and to help coordinate new studies. When not in the field, Goldberg is in her office fielding queries on medical issues ranging from adherence to protocols. “I provide the data,” she says. “How that data is used is based on doctors’ clinical judgment.”

Unlike sales reps, who follow tightly regulated scripts, medical liaisons can provide off-label info (for conditions other than those approved by the Food and Drug Administration) on the premise that more data mean better care. Not surprisingly, drug companies today employ teams of medical liaisons (starting salaries can reach $80,000) to educate “thought leaders” -- PR-speak for influential physicians and advocates -- about drug benefits. Goldberg, who spent 15 years as a nurse, prefers to frame the job in human terms. “My first priority has always been a patient’s well-being,” she says. “That gives me the foundation and credibility to do my job.”

Isabel McCoy: Registered Nurse, San Francisco General Hospital, San Francisco

It happened seven years ago during her rounds. Isabel McCoy, a veteran nurse at San Francisco General’s model AIDS ward, pricked herself with a needle. “It was really scary,” the Salvadoran native says. The hospital offered her AZT, but she decided to take her chances with a known virus rather than an unknown toxin, and remains HIV negative. For McCoy, a devout Catholic, such leaps of faith are routine. She’s seen healthy patients inexplicably nosedive toward death and dying patients make miraculous recoveries.

Of the thousands of HIVers she has nursed, she became attached to many; when one dies, crying becomes a part of the job. “There have been many moments...,” she recalls, her voice trailing off. McCoy is on 12-hour duty daily for seven days, every two weeks, and gets paid about $60,000 a year. The money is pretty good, she says, but her satisfaction comes from helping her patients. “You give a part of yourself to care for someone.” The first-ever AIDS ward recently merged with the hospital’s cancer unit, reflecting a national decline of AIDS deaths.

Erise Williams Jr.: Executive Director, Blacks Assisting Blacks Against AIDS (BABAA), St. Louis

“I’m married to this cause, which is probably why I don’t have a partner,” Erise Williams Jr. says about his decade-long affair with BABAA, Missouri’s only black-run AIDS agency targeting that community. Driven by a mix of personal loss and entrepreneurial gusto, Williams, 34, turned $12,000 in grants in 1990 into a $1.2 million agency with 28 staffers, bucking the national trend of poorly funded and staffed black agencies.

His first priority? Battling deep-seated suspicions locals have toward public-health edicts. “Condoms are a big issue for African-American men,” Williams says, “no pun intended.” After serving for years without pay, delivering prevention messages to churches and gay bars, Williams, recently allowed himself a raise: $70,000 a year and, for the first time ever, health benefits.

J. Walton Senterfitt: Prevention Coordinator, Centers for Disease Control and Prevention, Atlanta

Walt Senterfitt is not your typical government scientist. He wears Hawaiian shirts and Teva sandals to work, freely discloses his HIV status (positive) and AOL cruising name (DadMaster7), and was once arrested during an ACT UP demo against the CDC years before the agency employed him. Senterfitt, 56, runs a controversial project to create prevention campaigns for people already infected. In one TV spot he helped create, a shirtless man says to the camera, “I believe in taking responsibility...HIV stops with me.”

Senterfitt’s $60,000-a-year job hasn’t been a breeze. Activists have accused Senterfitt of selling out; colleagues call him too radical. “I have accepted that I need to moderate my language in order to do the work,” says the same man who has been busted 19 times for civil disobedience. “But eventually I will get fired.”

Orlando-Gerard Jimenez: AIDS Benefit Coordinator, Kaiser Permanente, San Francisco

Orlando-Gerard Jimenez is a professional HMO customer. As an AIDS benefit coordinator at Kaiser, the nation’s largest not-for-profit HMO, his job is to link HIV positive subscribers to a Byzantine array of public and private benefits, from ADAP assistance to Kaiser’s own. “I try to trouble-shoot,” says Jimenez, who earns $42,000 a year. “These programs are so complicated, it can be devastating to patients.” In practical terms, Jimenez talks to dozens of HIVers a day, advising them on insurance options as well as advocating on their behalf with government paper-pushers.

In the HMO age, penny-pinching and restricted access to services prevail. “When I first came here, I thought I would have to fight Kaiser,” says Jimenez, who started in 1999. “I’ve been pleasantly surprised.” Still, he recognizes that his services are limited to “the cream of the crop” -- those who can afford to pay Kaiser’s high monthly premiums. “I don’t know what happens to poor people,” Jimenez says. Cynics might argue that he’s there to fatten the company’s bottom line by keeping customers happy, but Jimenez disagrees: “Our success is measured by our members’ satisfaction.”

-Denny Lee

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