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**The science of side effects
(or, who's afraid
of 3T3-F44A2 cells?)**

300

The science of side effects (or, who's afraid of 3T3-F44A2 cells?)

Mark Mascolini



Basic science easily trumped clinical research in the slide sessions of the Lipodystrophy Workshop—for the first time in that meeting's four years. Is there a message there? Maybe two: First, bench work has started to crack some of the cellular secrets that account for antiretrovirals' metabolic toxicities. And second, clinical progress in managing these side effects continues to be slow. And what about the lap swimmers in the above photo? Please turn to page 300.

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REPORT FROM THE PRESIDENT

The more things change...

José M. Zuniga

One cannot help but note how different the battle against AIDS is today from what it was at the dawn of the epidemic—and yet how similar in other respects. In recent years, there has been a greater awareness of our collective need to assist men, women, and children with AIDS, especially those in the developing world. That realization has prompted numerous changes, the most significant of which was the launch of the Global Fund to Fight AIDS, Tuberculosis, and Malaria. Yet, less than a year later, the political apathy that has persistently shadowed AIDS has reared its ugly head: the Global Fund may in fact be insolvent by 2003.

When it began operation ten months ago, the Global Fund seemed an example of the conviction needed to take the difficult, but entirely realizable steps necessary to prevent the unnecessary suffering and premature death of hundreds of millions. Yet, as has been commonplace in the history of AIDS (and other endemic diseases of the developing world), investing in health for all has not been a priority, and the most concerted effort the world community has pulled together to prevent a global catastrophe – with mortality levels easily tripling or quadrupling the number of World War II casualties—may well be ignored into extinction.

The Global Fund was the result of a unanimous vote of world leaders gathered for the historic United Nations General Assembly Special Session on HIV/AIDS in June 2001. Such international cooperation was perhaps the most promising aspect of the Global Fund, because, when drawn from the combined resources of the world's

wealthier nations and philanthropic institutions, the US\$10 billion that experts agreed would be needed annually to assist developing countries in combating the three diseases was a very manageable amount. Cooperation in theory, however, has not materialized into cooperative giving. To date, pledges to the Global Fund have totaled US\$2.1 billion, almost all of it in the form of promised money, to be delivered over the next several years. But because the need is so great, and on the hope that the parsimonious giving trend will be reversed, the Global Fund has already committed to disbursing twice that much over roughly the same period.

There is no question that the global fight against infectious disease requires at least this much monetary support. The World Health Organization and the Joint United Nations Program on HIV/AIDS foresee US\$6.5 billion in “urgent needs” that the Global Fund should address in 2003. By 2005, they estimate that US\$10 billion will be needed. And, as disease continues to spread, and medical infrastructure and organizational experience improves so that money may be spent more effectively, that number will increase to US\$15 billion by 2007.

We must remember that even this higher figure—US\$15 billion—is infinitesimal in comparison to the total of what the world's governments spend in a year. When the Global Fund's estimated needs for 2005 are divided among the wealthiest nations in shares based on each country's percentage of the world gross domestic product (GDP), the United States' share is about US\$3.5 billion, Japan's is US\$1.6 billion, and Germany's is US\$660 million. Rounding out the top five, the United Kingdom and France's shares would be

approximately US\$500 million and US\$450 million, respectively.

It is important to place those numbers in perspective. For example, US government revenues and expenditures in a given year are each about US\$1.8 trillion (remember, a trillion is a thousand billion). The US government now spends about US\$400 billion a year on national defense in peacetime, and that number is exponentially increasing given the ongoing war on terrorism (not to mention Iraq). The US share of the US\$10 billion needed for the Global Fund in 2005 would, therefore, be far less than one percent (0.2 percent) of the government's annual expenditures.

Of course, there are many worthy causes, including domestic causes, on which governments can and should spend their taxpayers' money. And a decision to spend on foreign aid can be unpopular with voters. It is undeniable, however, that the equal-share funding levels described above are manageable and could be instituted with very minimal strain on the budgets of the governments called upon to practice either *noblesse oblige* or enlightened self-interest, since the AIDS pandemic is not only a threat abroad, but also to domestic health and security.

At some point, a statement of support against AIDS (and other endemic diseases afflicting our world) without a check in the mail becomes disingenuous. As the nations of the world realized in June 2001, the Global Fund may be our best chance to stem the tide of disease that, as effectively as weapons of mass destruction, is decimating millions. ■

José M. Zuniga is President of the International Association of Physicians in AIDS Care and Editor-in-Chief of the IAPAC Monthly.



P E R S P E C T I V E

The business of medical research

Jeffrey P. Kahn

The October 24, 2002, *New England Journal of Medicine* contained a study of whether and how medical schools enforce guidelines to help reduce inappropriate influence by drug companies on medical research they fund.

What the authors found is disturbing for anyone who thinks medical research is immune from the kinds of biases seen recently in the business world. Of more than 100 medical schools surveyed, less than 5 percent had rules that guaranteed researchers access to all research results, that established independent committees to oversee studies, or that required that research results be allowed to be published.

Allowing companies so much say in how research is performed or reported is not good for research subjects, patients, or society. So how did we get to this point, and what can we do about it?

Restrictions on researchers

The problem is that when drug companies fund research, they may limit what the researchers can do. These restrictions introduce a conflict for researchers between making decisions based on science and agreeing to decision-making limits to get their research funded by the drug company.

These conditions can include “veto” by the company on the sharing or publication of study results, which is more likely to happen when the results are not positive.

The problem is that negative findings could be useful in advancing medical research and treating patients, especially if the research shows that a particular product is harmful.

Preventing conflicts of interest

Numerous organizations and the federal government have issued guidelines regarding financial conflicts of interest for

researchers—what financial interests in the research are acceptable for investigators before they may bias the researchers’ judgment.

The current issue is a twist on the same theme: Do researchers owe their commitment to the research whatever the results? Or do they owe their allegiance to the company that funds the research?

The International Committee of Medical Journal Editors helped answer that question by announcing that many leading medical journals would only publish articles submitted by researchers who could attest that they had control over the research data and what should be done with it. But as the current study shows, precious few medical schools actually require such conditions.

Who is minding the research shop?

Both researchers and universities depend on research funding, so it is difficult for them to govern themselves always, especially in a competitive research market. So rules must come from elsewhere.

The US Office of Human Research Protections (OHRP) is a likely source, and the office has considered issuing guidelines on research conflicts of interest. But since the OHRP’s Director, Greg Koski, just announced his resignation after less than two years on the job, it is unclear whether the office has the clout to do so.

Whether watched over by the government or not, universities need to protect their researchers by insisting that contracts with drug companies include provisions for appropriate access to research data, limits on restrictions that companies can impose on the use of the data, and clear policies for who owns the data generated by the research. Since so much medical research is performed in university settings, an agreement by the university community to live by such rules can create a standard that drug companies will respect.

A national survey of provisions in clinical-trial agreements between medical schools and industry sponsors

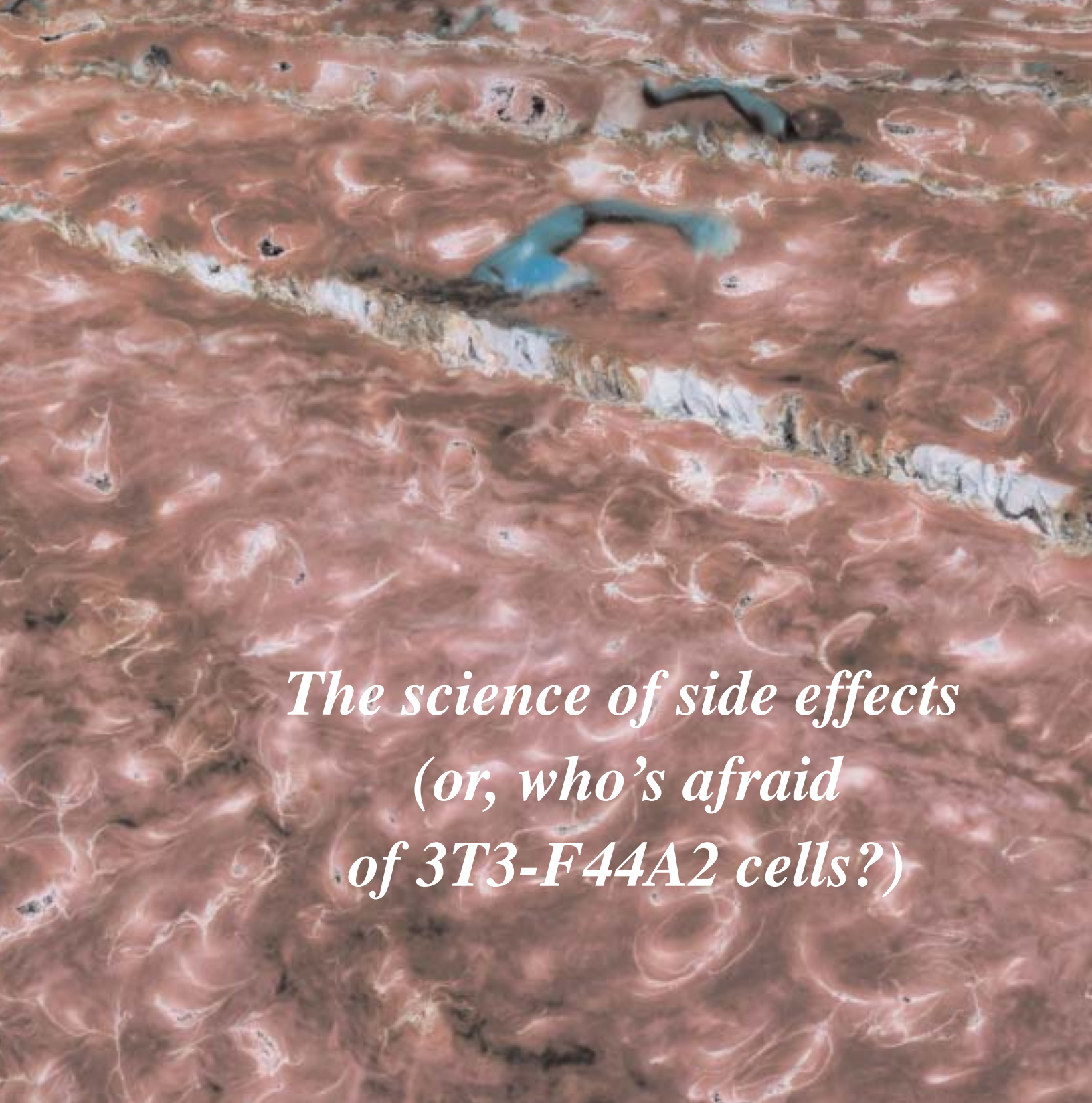
K Schulman, DM Seils, JW Timbie, J Sugarman, et al.

Background: Concerned about threats to the integrity of clinical trials in a research environment increasingly controlled by private interests, the International Committee of Medical Journal Editors (ICMJE) has issued revised guidelines for investigators’ participation in the study design, access to data, and control over publication. It is unclear whether research conducted at academic institutions adheres to these new standards. **Methods:** From November 2001 through January 2002, we interviewed officials at US medical schools about provisions in their institutions’ agreements with industry sponsors of multicenter clinical trials. A subgroup of the respondents were also asked about coordinating-center agreements for such trials. **Results:** Of the 122 medical schools that are members of the Association of American Medical Colleges, 108 participated in the survey. The median number of site-level agreements executed per institution in the previous year was 103 (interquartile range, 50 to 210). Scores for compliance with a wide range of provisions—from ensuring that authors of reports on multicenter trials have access to all trial data (1 percent [interquartile range, 0 to 21]) to addressing the plan for data collection and monitoring (10 percent [interquartile range, 1 to 50])—demonstrated limited adherence to the standards embodied in the new ICMJE guidelines. Scores for coordinating-center agreements were somewhat higher for most survey items. **Conclusions:** Academic institutions routinely engage in industry-sponsored research that fails to adhere to ICMJE guidelines regarding trial design, access to data, and publication rights. Our findings suggest that a reevaluation of the process of contracting for clinical research is urgently needed.

New Engl J Med 2002;347:1335-1341

We must do everything we can to avoid what is beginning to sound like the “Enron-ization” of medical research and to live by a commitment to making sure that what is produced is the best information that research can provide rather than the best information that money can buy. ■

Jeffrey P. Kahn is Director of the Center for Bioethics at the University of Minnesota, and author of the bimonthly CNN Interactive column “Ethics Matters.”

An aerial photograph of a coastline. The water is a deep blue, and the land is a mix of brown and green, suggesting a natural, somewhat rugged environment. The coastline is irregular, with several inlets and peninsulas. The text is overlaid on the lower half of the image.

The science of side effects (or, who's afraid of 3T3-F44A2 cells?)

Mark Mascolini

Every morning from 7 till 9 San Diego's Hotel Del Coronado ("the Del" to locals) hosts an allegory on risk taking in scientific research. Of course the Del's crackerjack convention staff is much too savvy to call it that.

Instead they present the allegory in the guise of a "lap swim" in the big shoreside pool.

This works out well because most of the Del's vacationing guests are still abed at 7 AM, and most of them don't like to swim in the fog, the prevailing atmospheric at that hour on the Pacific coast. But plenty of hydrophilic meeting attendees, stripped

to their hydrophobic hides, show up to put in their laps—including a few from the 4th Lipodystrophy Workshop. After four or five jump in, the staff's clever planning becomes clear. No, the towel boy isn't smiling because he's paid to; he's smiling because the allegory of scientific research has begun to unfold.

Instead of roping off the pool's entire length in lap lanes, the staff deploys only two lines, yielding two lanes. Further, they have painted no lap lines on the bottom. Two swimmers, unnerved by the foggy, lineless pool, head straight for the lanes and stay there, crawling contentedly. A slightly more daring duo follows, one sighting off the outside lap rope, the other off the far wall, to stay on track. The most adventurous plunge into the pool's chartless center, hoping to steer a straight course despite fog, lack of guidelines, and the pother of less bold paddlers. Some of them swim straight as dolphins. Others meander aimlessly. Late arrivals jump cheerfully into the froth, contributing nothing but congestion.

Though tender in years, the towel boy can probably guess which swimmers will play it safe, which will push the envelope just a little, which will take the boldest plunge, and maybe even which will succeed when they do. He's seen enough fog swimmers to spot the telltale traits. It's not as easy guessing which scientists will set a true and steady course, though one might discriminate the daring from the diffident.

Research into the metabolic disturbances of HIV and antiretrovirals has reached the point where players abound. Some favor the laid-back backstroke, others the gaudy butterfly, and others the relentless Australian crawl. Some stick to established lanes; some swim uncharted waters. A few pace setters have emerged, even snagging some early trophies. But it's much too soon to tell which of the boldest bathers have the grit, guile, and good luck to prevail.

The quickening pace of their exploits set the tone at this year's Lipodystrophy Workshop, where basic research commanded the center lanes for the first time in this meeting's four years (Table 1). Whereas cohort studies, case series, and clinical trials accounted for a big majority of slide talks in 1999, 2000, and 2001, they filled fewer than one third of the slide slots in 2002. Meanwhile, basic research—defined here as studies in engineered cells—surged from a bare 5.5 percent of

Table 1. Basic research comes to the fore at the Lipodystrophy Workshop

Workshop year	Type of study, n (%), in oral abstracts				
	Human	Human tissue	Animal	Cell	Statistical analysis or assay
2002	9 (31)	3 (10)	2 (7)	12 (41)	3 (10)
2001	21 (70)	3 (10)	2 (6)	4 (13)	0
2000	21 (64)	2 (6)	3 (9)	7 (21)	0
1999	16 (89)	0	0	1 (5.5)	1 (5.5)

talks in 1999 (one presentation) to 41 percent this year (12 talks). On top of that, three other PowerPoint excursions featured statistical analyses or assays, and two probed animal models of drug toxicity.

People enduring the metabolic malfeasance of antiretrovirals, and the clinicians who care for them, may see this fountainhead of research in two ways. On the one hand, it means the study of antiretroviral-linked metabolic disorders has matured. Now the unglamorous grunt work of cell sorting and real-time fluorescence can eke out data that may define actual mechanisms, instead of cohort-calculated "associations." And finding mechanisms not only points the way to remedies, it also helps define risk, progression, and prognosis.

On the other hand, studies of 3T3-F44A2 cells sure lack the sizzle of a big randomized trial pitting drug suspects A and B against drug suspects X and Y, or even a tidy case-control exercise that ferrets out risky dietary indiscretions or genetic jeopardies. Of course clinical trials and other human studies must rest on hypotheses, and well-reasoned hypotheses often rely on primal benchwork. Yet understanding clinical trials can seem (the operative word) so much easier than understanding what a drug may or may not do to a dishful of hepatocytes. When significantly more people taking certain drugs in an adequately powered randomized trial end up with a side effect of interest, prescribers make decisions. But in cell studies questions can outnumber conclusions:

- Does the drug dose approximate drug exposure in living human tissues?

- Have the researchers accurately measured drug concentrations in cells or tissues?
- If an intracellular reaction is measured at peak concentration, will a person with concentrations scaling between two peaks and troughs daily have the same reaction?
- Does exposure to a single drug (indinavir is a popular subject) reflect what happens when a person takes that drug with others (a ritonavir boost, say, plus d4T and 3TC)?
- Does the mouse study design compensate (or overcompensate) for that model's peppy metabolism?
- What about protein binding?
- And so on.

From bench to bedside

Worrying too much about these pitfalls would freeze research on the starting block, but the pitfalls can't be ignored. Take, for example, the ambitious study by Jacqueline Capeau (Saint-Antoine Hospital, Paris), an acknowledged leader in this field who tied lipodystrophy in people taking PIs to lower levels of sterol regulatory element binding protein-1 (SREBP-1).¹ Her new study sought to discern the effect of didanosine (ddI) and stavudine (d4T) on adipocytes when given with indinavir [abstract 9, L6*]. Among the findings:

*Abstracts from the Lipodystrophy Workshop are published in the 2002 volume of *Antiviral Therapy*. Citations here give the abstract number and the journal page number, which is preceded by an L. Workshop abstracts are online at [http://www.intmedpress.com/journals_contents_avt7\(3\)cont.cfm#lipo](http://www.intmedpress.com/journals_contents_avt7(3)cont.cfm#lipo). Abstract numbers beginning with an H are from the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held September 27-30 in San Diego.

- Although ddI and d4T did not alter indinavir-impelled fat cell differentiation, they lowered those cells' triglyceride content, a lipotrophic effect.
- The two nucleosides partly reversed indinavir-induced insulin resistance.
- Together, indinavir and d4T (but not ddI) promoted apoptosis (cell death) additively.
- Rosiglitazone, a PPAR-gamma agonist, almost totally prevented the adverse effects of indinavir and ddI/d4T (alone or together) on lipid content and apoptosis.

Ultimately these findings may say more about the interactions of nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) than the best-designed multinational placebo-controlled trial, because the findings may explain not only what happens, but how. Independent confirmation of the results would make them even more compelling.

But clinicians can't look at these data and decide, for example, that ddI/d4T plus indinavir makes sense because that lipotrophic risk may be offset by appeased insulin resistance. A representative of these NRTIs' maker was prompt to observe that the peak concentrations achieved with 10 μ M of each drug may reflect peaks in humans. But no human goes through the day with peak drug levels. Session cochair Steven Grinspoon (Massachusetts General Hospital) noted that technicians administered the rosiglitazone along with ddI and d4T in these experiments, not as a clinician may someday use rosiglitazone, months and months after an NRTI's lipotrophic effects become evident. True, Capeau replied, but her bench-to-bedside cogitation had already clicked to the next implication: Should people start taking glitazones when they start taking potentially lipotrophic drugs?

Leagues away on the other side of the research spectrum sat a single case report proffered by Stefan Mauss (Center for HIV and Hepatogastroenterology, Düsseldorf). In its humble way, this simple, stark case study probably speaks more directly to HIV clinicians than the most elegant and provocative lab work. Mauss chronicled the story of a trim young man (there is a picture) who took two courses of postexposure prophylaxis after risky sex with his HIV-infected partner [abstract 77, L51].

He did not become infected. But six weeks after his second three-week course

of d4T, lamivudine (3TC), and efavirenz, his abdomen ballooned into the classic picture of central lipohypertrophy. CT scans disclosed a large depot of visceral adipose tissue. Although lipids and blood glucose remained normal, the central fat buildup persisted to the time of Mauss's report, five months after the man took his last antiretroviral. Mauss advanced the case as "a limited proof of principle that the changes in adipose tissue [characteristic of lipohypertrophy] are caused by antiretroviral treatment rather than HIV infection itself."

Perhaps just as disturbing as this sudden-onset lipohypertrophy in an antiretroviral-treated man without HIV infection are the drugs he took—two nucleosides and the nonnucleoside (NNRTI) efavirenz, not a PI. Is the case just a wretched quirk? Or will inspired benchwork have to sort out how six weeks of d4T, 3TC, and efavirenz may rile adipocytes? The case seems unlikely to touch off a wholesale abandonment of efavirenz. But it shows how an utterly straightforward, *n*-of-one study can simultaneously make a shocking clinical point and raise questions that can be fathomed only by deep-diving basic research.

From bedside to bench

Results of large clinical trials can be less ambiguous than Stefan Mauss's disturbing case report. Take, for example, AIDS Clinical Trials Group (ACTG) protocol A5005s, reported by Michael Dubé (Indiana University, Indianapolis) [abstract 27, L18]. Although a mere substudy of ACTG 384, A5005s had 330 participants randomized to take zidovudine (ZDV)/3TC or ddI/d4T plus nelfinavir, efavirenz, or both. Intent-to-treat and on-treatment analyses showed a significant drop in DEXA-measured limb fat in the ddI/d4T group after 48, 64, and 80 weeks of follow-up. Both the ddI/d4T group and the ZDV/3TC group, who started the study with no antiretroviral experience, gained limb fat in the first 16 weeks, then started losing fat. At week 48 the limb fat in the ddI/d4T group was down 0.28 kg (7.5 percent), while fat in the ZDV/3TC group still stood 0.26 kg above baseline (4.7 percent) ($P = 0.027$). The ZDV/3TC group continued to lose peripheral fat through week 80, but the difference from baseline had not reached statistical significance at that point.

People assigned to nelfinavir lost a median 0.92 kg of limb fat (18 percent) by week 80, a significant change from baseline ($P = 0.019$). People randomized to efavirenz lost a median 0.50 kg (10.7 percent) at that point, but that change from baseline lacked statistical significance. Whites did not differ from nonwhites in limb fat changes. Trunk fat tended to rise in all treatment groups. Total and lumbar bone mineral density did not change significantly in any group.

The results of this randomized trial add to the pile of evidence implicating d4T in peripheral lipoatrophy. And more such evidence came in the next report, a longitudinal study of 27 people starting their first triple-drug regimen with d4T and 26 starting with ZDV [abstract 28, L18]. Measuring limb fat as a percentage of body mass index, David Nolan (Royal Perth Hospital) used DEXA scans to chart a drop from 22 percent to 13 percent after two years in the d4T group ($P < 0.005$) and from 22 percent to 19 percent in the ZDV group, a nonsignificant change. Equivalent proportions of both groups took PIs or non-PI regimens, and limb fat changes did not differ between PI and non-PI groups.

Studies like these, and others showing compound toxicities with ddI/d4T,² led clinical investigator Judith Currier (University of California, Los Angeles) to propose removing ddI/d4T from guideline lists of preferred nucleoside pairs.

At the same time, David Nolan reminded Workshop attendees, one can't ignore nondrug factors that promote lipodystrophy. In another study he confirmed earlier findings³ that a polymorphism in tumor necrosis factor alpha (TNF-alpha) spurs a quicker onset of lipodystrophy [abstract 26, L17]. He found the TNF-alpha promoter polymorphism 238G/A in 13.1 percent of 220 Western Australian Cohort members, all of them white. A Cox proportional hazards analysis figured that heterozygosity for the polymorphism raised the risk of clinically identified lipodystrophy 1.73 times ($P = 0.041$) and did so independently of age, duration of NRTI therapy before highly active antiretroviral therapy (HAART), or duration of d4T therapy.

How this polymorphism promotes lipodystrophy remains an open question. But TNF (or cachectin) has a long-established role in wasting (or cachexia). And work by Pere Domingo (Hospital de la

Santa Creu i Sant Pau, Barcelona) traced a link between adipocyte death and circulating levels of two soluble TNF receptors in 45 HIV-infected men and women with lipoatrophy [abstract H-1920]. Receptor levels were significantly higher in those with diffuse apoptosis than in those with moderate, focal, or no apoptosis. In another study, though, levels of soluble TNF receptors did not correlate with lipoatrophy in people with HIV (see the next section).

The four related studies just summarized span the gamut from straightforward clinical trial, through simple longitudinal analysis, back to a bed-lab interface exploring genes or cytokines. The murky origins of metabolic disorders, and their miasmatic evolution—especially in people taking toxic drugs—mean HIV clinicians must grapple with the hard science, get knee-deep in adipocytology, and recall lost lessons in dyslipidemia, never forgetting two decades of revelation in immunology. And what better launching pad than leptin?

HARD SCIENCE

On day one of the Lipodystrophy Workshop, no word leapt from more speakers' lips than leptin. Discovered only eight years ago, touted and dismissed as a panacea for obesity, this potent peptide has become the darling of non-HIV lipodystrophy research. Inevitably, leptin landed on the HIV research agenda, and workshop organizers allotted it a keynote lecture, a plenary lecture, and a slide talk—all in the meeting's first session.

- *What is leptin?* Leptin is the afferent signal in a negative feedback loop linking nutrition to other physiologic systems, offered keynote speaker Jeffrey Friedman (Rockefeller University, New York).

- *An example might help.* Friedman summoned a mouse model to clarify: When leptin gets switched off, as it is in leptin-deficient *ob/ob* mice, the animals suffer a perceived state of perpetual starvation. So they eat all the time and get fat. Very fat. Severely leptin-deficient humans also become obese. Leptin-replacement therapy quiets their overeating, and they lose weight.⁴

- *Where does leptin come from?* Adipocytes secrete leptin.

- *Where does lipodystrophy come in?* In people without HIV infection, generalized

lipodystrophy can drastically lower leptin levels and promote overeating. Four months of recombinant leptin taken by nine women with severe lipodystrophy and abysmal leptin levels (all below 4 ng/mL) improved glycemic control (eight of the women had diabetes), hypertriglyceridemia, and hepatic steatosis.⁵ They all cut their daily calories dramatically. In these people leptin proved a potent insulin sensitizer, but no one can explain why.

- *But people with HIV lipodystrophy are not typically obese.* Right. And most obese people, Friedman noted, have leptin levels much *higher* than lean people. Rather than leptin deficiency, he suggested, they must have some insensitivity to the hormone. When lipodystrophy experts like Friedman and Stephen O'Rahilly⁶ (University of Cambridge) talk about this heterogeneous group of disorders, they are talking mostly about fat *atrophy*. (When lipodystrophy experts like Carl Grunfeld talk about the syndrome in people with HIV infection, they are talking mostly about atrophy too. See "Art and artifice" below.) This "absence of adipose tissue," Friedman noted, is also linked to leptin deficiency, as well as to insulin resistance and diabetes. Leptin replacement in atrophic mice reversed their insulin resistance and diabetes.⁷

O'Rahilly summarizes things this way⁶:

Congenital leptin deficiency ↓ Principal abnormality: Massively expanded fat mass ↓ Therapeutic impact of leptin: Reduces fat mass	Generalized lipodystrophy ↓ Principal abnormality: Excess fat cannot be stored in adipose tissue ↓ Therapeutic impact of leptin: Reduces excessive fat storage in nonadipose tissue and so ameliorates insulin resistance
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"Thus," O'Rahilly concludes, "we now know of two distinct human diseases where the correction of near aleptinemia is of major therapeutic benefit."

- *So will leptin work in people with HIV lipodystrophy?* It all comes down to leptin levels. O'Rahilly again: "The metabolic

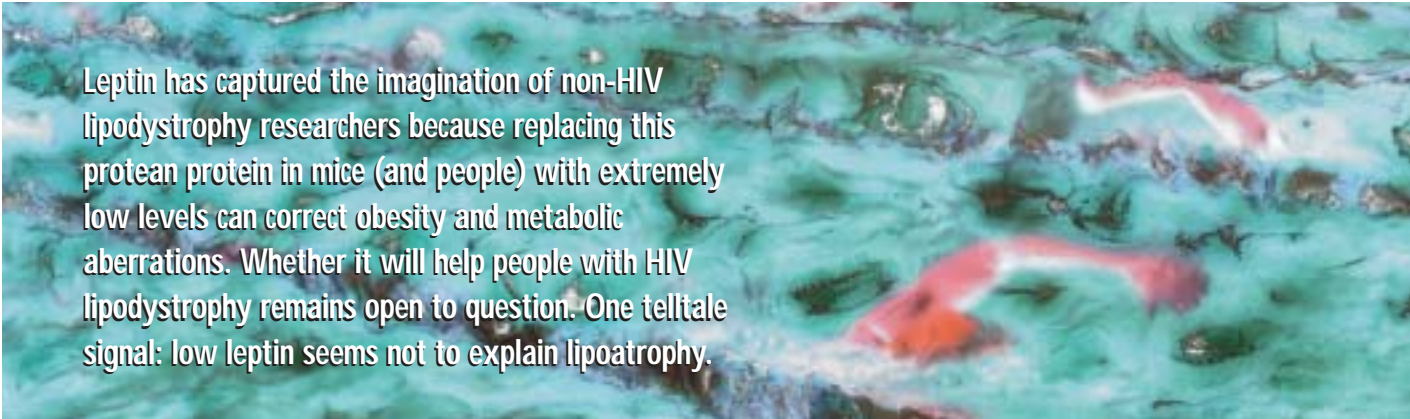
consequences of generalized lipodystrophy are unlikely to be entirely attributable to very low levels of circulating leptin."⁶ (Note that the two groups that benefited from leptin replacement shared one trait: "near aleptinemia.") So, O'Rahilly goes on, "the clinical response to leptin therapy is likely to be partial at best."

A study by Grace McComsey (Case Western Reserve University, Cleveland) may offer the clearest hint so far about the potential for leptin replacement in HIV-infected people with lipoatrophy [abstract 78, L51]. Her retrospective analysis of 137 people starting their first antiretrovirals suggested leptin replacement will not help most lipoatrophic people with HIV because low leptin probably did not cause their atrophy.

After a median follow-up of 1,045 days, 40 people in this group had clinically apparent lipoatrophy, and after a median 743 days, 97 did not. In a univariate analysis, several factors, including lower leptin, favored emergence of lipoatrophy:

- Older age: 43 years in those with lipoatrophy versus 37 years in those without it ($P < 0.001$)
- Lower body mass index before therapy: 23 versus 25 kg/m² ($P = 0.05$)
- Longer treatment duration: 1,104 versus 845 days ($P = 0.01$)
- Higher use of PIs: 90 percent versus 68 percent ($P = 0.007$)
- Lower use of NNRTIs: 15 percent versus 43 percent ($P = 0.001$)
- Pretherapy leptin level: 5 ± 4 ng/mL versus $11 + 14$ ng/mL ($P = 0.017$)

But when McComsey parsed those parameters in a multivariate analysis, only older age, treatment duration, and lower pretreatment body mass index independently predicted lipoatrophy. The results, she concluded, do not support an independent role for leptin in lipoatrophy, perhaps because the low leptin levels merely reflect the lower pretreatment body mass index in the lipoatrophy group. Some people with lipoatrophy clearly had severely low leptin levels, as low as 1 ng/mL. But the average leptin level in the whole lipoatrophy group, 5 ng/mL, falls above the severe deficits measured in seronegative people who have benefited from leptin replacement so far. Levels of soluble TNF receptors, which correlated with fat cell death in Pere Domingo's study (above),



Leptin has captured the imagination of non-HIV lipodystrophy researchers because replacing this protean protein in mice (and people) with extremely low levels can correct obesity and metabolic aberrations. Whether it will help people with HIV lipodystrophy remains open to question. One telltale signal: low leptin seems not to explain lipoatrophy.

did not correlate with atrophy in McComsey's analysis.

• *But could leptin help correct antiretroviral-induced metabolic abnormalities?* One workshop study addressed that question. And, at least for PI-exposed mice, the answer was yes. Tara Riddle (University of Cincinnati) tested both leptin and dietary polyunsaturated fatty acid (PUFA) in mice with ritonavir-induced lipid abnormalities [abstract 5, L3]. PUFA didn't work. Leptin, at a dose of 5 µg daily, significantly lowered cholesterol (by 21 percent) but had little effect on triglycerides. Brown fat and liver mass both increased with ritonavir and decreased with leptin.

Leptin wasn't the only item on the workshop's basic research agenda. Given McComsey's findings, it may not even be the most important for people with HIV lipodystrophy. Several other studies stood out:

i. Genesis

Genesis of fat cells slowed to a crawl when Simon Jones (University of Liverpool) daubed 3T3-F44A adipocytes with nelfinavir, saquinavir, or ritonavir, with or without ZDV or d4T [abstract 3, L2]. With the method Jones used, measuring glycerol-3-phosphate dehydrogenase, indinavir curtailed adipogenesis less. But indinavir synergized with ZDV or d4T in slowing adipogenesis. The PIs also boosted levels of **TNF-alpha and IL-6**, which vex adipocyte metabolism. Jones's colleague Omar Janneh showed that ZDV and d4T phosphorylated to their active metabolites in cultured fat cells, but they didn't inhibit adipogenesis or promote lipolysis—the spilling of fatty acids from adipocytes into the circulation [abstract 2, L1]. PIs slowed glucose uptake in fat cells, in this order: indinavir > saquinavir > ritonavir > nelfinavir.

ii. Lamentation

Jacqueline Capeau's work shows that altered expression and nuclear localization of a transcription factor, sterol regulatory element-binding protein-1 (SREBP-1), may explain why indinavir stymies adipocyte differentiation and response to insulin.¹ Pursuing these leads in 3T3-F44A2 cells, she found that indinavir stifles maturation of **lamin A/C**, which interacts with SREBP-1 and makes up part of the fibrous web lining the shell of fat cell nuclei [abstract 1, L1]. The resulting disruption of nuclear architecture could alter adipocyte function. People with a much-studied non-HIV insulin-resistant lipodystrophy—familial partial lipodystrophy—have mutated lamin A/C.

iii. Over PPAR

Comparing subcutaneous fat from the thighs of antiretroviral-treated people with lipoatrophy, from antiretroviral-naive people without lipoatrophy, and from healthy controls without HIV infection, Ellen Li (Washington University, St. Louis) found significantly higher levels of peroxisomal proliferator-activated receptor gamma (**PPAR-gamma**) in the lipoatrophic individuals than in the other groups [abstract 4, L3]. (Insulin sparks formation of new fat cells via PPAR-gamma.) Levels of lipoprotein lipase (a fat-splitting or lipolytic enzyme) also proved significantly higher in the lipoatrophy group than in the other two groups.

iv. Idle islets

Beta cells live to secrete insulin in the pancreas. They lie in the storied islets of Langerhans, and their failure foments **insulin resistance**. Measuring glucose-stimulated insulin secretion in mouse and rat islets and a murine cell line, Joseph

Koster (Washington University, St. Louis) found a dose-dependent muffling of insulin release with indinavir [abstract 6, L4]. Stopping indinavir unleashed insulin.

v. Zucker rats undone

Zucker rats become hyperglycemic at five to 10 weeks of age. By the time they're 14 weeks old, they have **diabetes**. Kevin Yarasheski (Washington University, St. Louis) shortened their disease-free days even more by giving them NRTIs (ZDV/3TC, ddI/3TC, or d4T/3TC), indinavir alone, or indinavir plus two NRTIs [abstract 7, L4]. Compared with rats taking placebo, those taking two NRTIs had significantly higher glucose levels by week six to seven. Adding indinavir to the NRTIs significantly boosted glucose by week three.

vi. Lesion lessons

PIs may promote **atherosclerotic lesions** without boosting lipid levels in plasma. That surprising proposal evolved from a study of mice who drank water spiked with low-dose amprenavir, indinavir, or ritonavir for eight weeks and ended up with significant cholesterol jumps inside peritoneal macrophages [abstract 11, L7]. The mechanism may be up-regulation of the CD36 receptor, which Richard Greenberg (University of Kentucky, Lexington) documented in both a human cell line and in the mouse macrophages. After eight weeks, atherosclerotic lesion area proved significantly higher in PI-exposed mice than in those who swilled only the PI-transporting vehicle. But similar studies by Sharon Walmsley (Toronto General Hospital), reported last year in *AIDS*,⁸ found that PIs *lowered* expression of CD36 in human monocytes and in cell lines.

vii. Art and artifice

Walmsley's discrepant finding (Greenberg attributed it to differing methods) was not the only challenge to these and other reports of basic research at the Lipodystrophy Workshop. Jacqueline Capeau, for example, doesn't know why SREBP-1 lands in the right nuclear niche in half of the adipocytes she studies but not in the other half. Omar Janneh acknowledged that his cell studies may have been too brief to spot the slowly-evolving mitochondrial toxicities of NRTIs. Kevin Yarasheski noted that the high antiretroviral doses he needed to outpace rapid rat metabolism (10 times the human dose) make it more difficult to extrapolate his results to humans.

But artificial experimental conditions cannot be divorced from the art of research—basic or clinical. Even big placebo-controlled trials set exclusion and inclusion criteria that can't be tacked to an HIV clinic's door. ("People with a CD4⁺ count under 100 cells/mm³ or HCV infection, please apply elsewhere.") And trial participants typically benefit from more rigorous follow-up and high-tech monitoring than harried clinicians can provide. Stepping down a rung to the cohort study, whether longitudinal or cross-sectional, greys outcomes even more.

No finer example of cross-sectional ambiguity emerged in the past year than divergent results of the EMEA lipodystrophy case-definition study⁹ and the Fat Redistribution and Metabolic Change in HIV (FRAM) Study.¹⁰ Both were cross-sectional. Both compared hundreds of lipodystrophy-afflicted "cases" with lipodystrophy-free "controls." Both pinpointed peripheral lipoatrophy as a distinguishing hallmark of HIV lipodystrophy. But the case definition study confirmed clinical impressions that central fat gains also separate people with HIV lipodystrophy from those without it, and FRAM did not.

Why the difference? A first step toward resolving this conundrum came at a roundtable scheduled in conjunction with the Lipodystrophy Workshop by the Forum for HIV Collaborative Research. A summary of that meeting will appear on the Forum's Web site, <http://www.hivforum.org>. But no one needs deep thinking and tension-packed panels (a fair description of the Forum session) to discern the glaring difference between these cross-sectional exercises. The case definition study com-

pared HIV-infected people without signs of lipodystrophy and HIV-infected people with one or more signs. FRAM compared people with HIV infection, randomly selected without regard to fat changes, and a non-HIV cohort in a big heart disease study.

Experimental choices, mind-numbing analyses, and consequently foggy findings can make human studies every bit as challenging as hard-core science. The lingo may be more familiar, but the doubts linger. Anyone who thinks otherwise will have an easy time with the following clinical questions:

1. Are protease inhibitors cardiotoxic?
2. Is HIV cardiotoxic?
3. Should you jump on—or off—the statin bandwagon?

Please answer in 50 words or less before reading the rest of this article.

HARD ARTERIES

Few questions have spawned bigger HIV cohorts than whether the virus or antiretroviral therapy heightens the risk of cardiovascular disease. The five largest cohort probes so far came up with different answers to this question. Two linked PI therapy to higher rates of myocardial infarction,^{11,12} and three did not.¹³⁻¹⁵ But two of the latter three studies did see more heart disease in people with HIV infection than in those without it.^{13,14} At the Lipodystrophy Workshop, and a few days later at ICAAC, these findings emerged:

- A record review found a higher risk of coronary heart disease in younger people taking antiretrovirals than in treatment-naïve HIV-infected people of the same age.
- The investigational protease inhibitor atazanavir reversed lipid leaps tied to nelfinavir.
- Several studies charted favorable lipid trends with efavirenz.
- Two studies found lofty lipids with d4T.

The record review involved 28,513 people with HIV infection who had no episode of coronary heart disease for at least one year after enrolling in California's Medi-Cal program [abstract 54, L37]. Splitting the cohort into those whose records showed antiretroviral prescriptions and those whose did not, Judith Currier

(University of California, Los Angeles) figured the risk of coronary heart disease in a multivariate analysis controlling for diabetes, hyperlipidemia, kidney disease, and hypertension. She also split the cohort into four age groups: 18 to 33 years, 34 to 49 years, 50 to 65 years, and 66 years or older. Only in the youngest group did antiretroviral therapy raise the risk of heart disease, 2.06 times ($P < 0.001$). Still, the incidence of heart disease among 18- to 33-year-olds was low: 1.08 cases per 100 patient years. In that age group and all others, hyperlipidemia, kidney disease, and hypertension independently raised the heart disease risk. Diabetes upped the risk in the three youngest age groups.

Currier did not try to define a link between PI therapy and heart disease, although two thirds of the 18- to 33-year-olds taking antiretrovirals had taken a protease drug. Three quarters of the three older age groups with treatment experience had taken PIs. A limitation of this analysis, Currier observed, is its inability to pin down other important variables, including smoking status, family history of heart disease, and precise lipid levels.

Yet other cohort comparisons suggest that men taking antiretrovirals don't differ much from the American men at large in cholesterol readings. In a plenary talk at the Workshop, statistician James Neaton (University of Minnesota, Minneapolis) compared four cohorts—two big heart risk studies in the general population, MRFIT and NHANES, and two CPCRA trials, SMART and FIRST. SMART enrolls antiretroviral-experienced people and FIRST recruits people naïve to antiretrovirals. Graphing cohort cholesterol levels of men by age, Neaton found that the lines for MRFIT, NHANES, and SMART essentially overlap. Despite their antiretroviral experience, SMART participants had cholesterol scores no worse or better than age-matched men from the general population. But the treatment-naïve FIRST men had cholesterol tallies substantially below those of men in the other cohorts. For example, the average reading for 40- to 44-year-old FIRST enrollees measured 160 mg/dL, compared with 200 to 210 mg/dL in the other cohorts.

These findings parallel pre-HAART data showing that HIV-infected people with and without AIDS had significantly

Table 2. **Lipid changes 12 weeks after switching from nelfinavir to atazanavir**

	At week 48	12 weeks after switch	P
Total cholesterol (mg/dL)	213	175	<0.001
Low-density lipoprotein cholesterol (mg/dL)	138	104	<0.001
High-density lipoprotein cholesterol (mg/dL)	46	48	—
Triglycerides (mg/dL)	156	108	<0.001

Source: Robert Murphy, abstract 15.

lower cholesterol levels than uninfected controls.¹⁶ Whatever the effects of HIV and antiretrovirals on lipids, Neaton reminded attendees, the ties between cardiovascular risk, HIV infection, HIV therapy, and individual patient traits remain hard to untangle. Although “cardiovascular events” now comprise only a small percentage of “adverse events” due to antiretrovirals, he counseled, the long-term cardiovascular consequences of therapy still lie somewhere over the horizon [see note 17]. And because many people taking antiretrovirals have histories thick with heart risk factors, the other side of the horizon may not be pretty.

More good lipid and insulin scores with atazanavir

Two 48-week studies of atazanavir in treatment-naïve people showed that this once-daily PI doesn’t share the lipid-inflating potential of other protease drugs.¹⁸ At the Lipodystrophy Workshop, follow-up in one of those studies showed that atazanavir can flatten lipid spikes inspired by nelfinavir [abstract 15, L10]. Robert Murphy (Northwestern University, Chicago) reported that people randomized to 1,250 mg of nelfinavir twice daily in an open-label comparison with once-daily atazanavir had a 25 percent leap in total cholesterol, a 23 percent gain in low-density lipoprotein cholesterol (LDL-C), and a 50 percent jump in triglycerides after 48 weeks. People randomized to 400 or 600 mg of atazanavir once daily, on the other hand, had only 5 to 8 percent elevations in these lipids through week 48.

After week 48, people taking nelfinavir could switch to 400 mg of atazanavir. Twelve weeks later, fasting lipids in switchers had dropped significantly (Table 2). Before the switch, 35 percent of those taking nelfinavir were candidates for antilipid therapy according to the National Cholesterol Education Program (NCEP);¹⁹ 12 weeks after swapping nelfinavir for

atazanavir, only 10 percent still ranked as candidates for lipid lowerers.

Despite the good lipid numbers with atazanavir, clinical signs of lipodystrophy do emerge in people taking this PI with d4T and 3TC, as they were in this trial. Clinicians noted 14 cases among people originally randomized to atazanavir and six among those who traded nelfinavir for atazanavir among the 346 people still in follow-up. Those low numbers may represent underreporting because the study protocol did not ask clinicians to track body shape changes. Murphy did not distinguish between peripheral atrophy and fat accumulation in this summary. Among people randomized to 400 or 600 mg of atazanavir, 23 percent and 35 percent respectively had grade 3 or 4 bilirubin elevations. In the nelfinavir-atazanavir switch group, 10 percent had high bilirubins. Murphy said hyperbilirubinemia rarely caused people to drop out of the study.

Analysis of 24-week trends in a placebo-controlled comparison of atazanavir and efavirenz plus ZDV and 3TC confirmed good lipid trends with both regimens [abstract 36, L26]. Michael Sension (North Broward Hospital District, Fort Lauderdale) reported modest gains in total cholesterol with atazanavir (1 percent) and efavirenz (20 percent), with means for both groups remaining below 200 mg/dL. Mean fasting LDL-C also stayed below the NCEP danger threshold of 130 mg/dL in both treatment arms.

Six-month data from this 810-person international trial showed that neither regimen induced insulin resistance as measured by fasting insulin, C peptide, and glucose concentrations. These markers hardly changed over 24 weeks with either treatment. Unlike some other protease inhibitors, atazanavir does not stymie insulin-mediated glucose traffic by inhibiting a transporter labeled GLUT-4. That may explain the lack of insulin resistance with atazanavir in this trial, Sension proposed.

Lipid subclass quiz (correct answer: efavirenz)

Clinicians who have done their lipid homework know that LDL-C, very low-density lipoprotein cholesterol (VLDL-C), and high-density lipoprotein cholesterol (HDL-C) particles come in large, small, or intermediate sizes. And which size predominates determines whether one’s risk of heart disease is low, intermediate, or high. Gary Simon and colleagues (George Washington University, Washington, DC) have been sizing up lipid particles in people taking efavirenz and other antiretrovirals. The good news for efavirenz partisans is that particle size and numbers look good in people taking this nonnucleoside. The good news for people with HIV and their clinicians is that Simon cooked up a nice particle size cheat sheet (Table 3).

Simon studied 22 treatment-naïve people, 15 starting nelfinavir and 17 starting efavirenz, in two different trials [abstract 14, L9]. So this is not a randomized comparison, and the number of study participants is small. Measuring lipid subclasses before treatment and periodically for the first 16 weeks, he determined that HIV infection itself conferred a low lipid-related risk in these people. Overall, LDL-C rose 45 percent in the nelfinavir group and 17 percent in the efavirenz group, while HDL-C rose 15.5 percent with nelfinavir and 35.4 percent with efavirenz ($P < 0.05$ for both comparisons). Looking at subclasses, Simon found that ominous small-particle HDL-C rose 44.8 percent with nelfinavir and 25.2 percent with efavirenz, while salutary large-particle HDL-C rose 8.2 percent with nelfinavir versus 40.9 percent with efavirenz ($P < 0.05$). The number of LDL-C particles rose 45 percent with nelfinavir and 11.7 percent with efavirenz ($P < 0.05$), again denoting a higher risk with the PI. Most people in both treatment groups were taking ZDV/3TC, although a few in the nelfinavir group were taking ddI/d4T.

Simon’s colleague Angelike Liappis confirmed these efavirenz-induced subclass shifts in a 16-week study of 17 treatment-naïve people starting the NNRTI with ZDV/3TC, or ZDV, 3TC, and abacavir [abstract H-1917]. LDL-C rose modestly though significantly from 98 to 114 mg/dL ($P = 0.0014$), but most of the gain came in the lower-risk large LDL-C particles (38 to 60 mg/dL, $P = 0.0234$). The total number of LDL-C particles

Table 3. Heart disease risk according to lipid particle size

	Subfraction	Particle size	Risk
VLDL-C	V12	Small	Intermediate ↑
	V34	Intermediate	Intermediate ↑
	V56	Large	High ↑
LDL-C	Number of particles		High ↑ with more
	L1	Small	High ↑
	L2	Intermediate	Intermediate ↑
	L3	Large	Intermediate ↑
HDL-C	H12	Small	Intermediate ↑
	H345	Large	Intermediate ↓

Source: Gary Simon, abstract 14.

Table 4. Heart rate and oxygen extraction with or without HAART or HIV

	On HAART (n = 15)	HIV+, no HAART (n = 15)	Seronegative (n = 15)	P
Peak heart rate (beats/min)	170.5	179.9	185.2	<0.05 for HAART vs seronegative
a-vO ₂ (volume percent)*	9.9	11.6	12.6	<0.05 for HAART vs other groups

Source: Todd Cade, abstract 16.

*Normal = 12 to 17 in sedentary people.

barely budged. Meanwhile, the more dangerous small HDL-C particles multiplied by only 26 percent, compared with a 40 percent jump in risk-lowering large HDL-C particles.

A 48-week open-label study of 10 girls and seven boys who traded a PI for efavirenz showed a sustained virologic response and healthier lipid profiles after the switch [abstract H-1081]. Sixteen of the 17 maintained a viral load below 50 copies/mL after taking efavirenz for 48 weeks, and the viral load stood at 62 copies/mL in the remaining child. Before the switch 12 children (71 percent) had triglyceride tallies above the 95th percentile for their age group, and five (29 percent) had cholesterol levels above the 95th percentile. After 48 weeks of efavirenz, average cholesterol fell from 203 to 175 mg/dL and only one child had a level above 200 mg/dL. LDL-C and triglycerides fell significantly ($P < 0.05$), and the group's cholesterol-to-HDL-C ratio fell 21 percent. Grace McComsey reported that no one stopped efavirenz because of side effects, though one child with a family history of epilepsy had a seizure.

PI therapy affects not only lipids in children, but also, as in adults, insulin sensitivity. Comparing 33 PI-treated children with 15 PI-naïve children, Ari Bitnun (Hospital for Sick Children, Toronto)

linked PIs with decreased insulin sensitivity among pubertal children ($P = 0.0163$) but not prepubertal children [abstract 8, L5]. In the whole group, three variables independently predicted lowered insulin sensitivity: older age ($P = 0.0002$), worse HIV immunologic category ($P = 0.0186$), and PI therapy ($P = 0.0333$).

Efavirenz came home with a decent metabolic report card in a long, single-center Spanish study. These 84 people beginning antiretroviral therapy with efavirenz had a modest but significant rise in total cholesterol (186 to 205 mg/dL, $P = 0.011$), a drop in uric acid (5.4 to 4.9 mg/dL, $P = 0.014$), and no substantial change in triglycerides or glucose after two years [abstract 46, L32]. Bernardino Roca (General Hospital of Castellon, Spain) did not report changes in LDL-C, HDL-C, or subclasses thereof.

Lipid liabilities with d4T

Two studies showed that d4T drives triglycerides and cholesterol in the wrong direction in treatment-naïve people starting a regimen including this nucleoside. Sharon Walmsley and colleagues randomized untreated people to start efavirenz or saquinavir/ritonavir (1600/100 mg once daily) [abstract 52, L35]. Fifty of them took d4T/3TC and the rest took a non-d4T NRTI combo, usually ZDV/3TC. Forty-

eight weeks later, both triglycerides ($P = 0.014$) and total cholesterol ($P = 0.021$) were significantly higher in the d4T group than in the non-d4T group. Lipid differences between people taking efavirenz and saquinavir/ritonavir did not reach statistical significance.

Outlining interim 48-week results of a placebo-controlled trial comparing tenofovir with d4T (plus 3TC and efavirenz), Joel Gallant (Johns Hopkins University, Baltimore) reported good immunologic and virologic results in both groups [abstract LB-2, ICAAC]. But triglycerides climbed an average 74 mg/dL in the d4T arm while staying flat in the tenofovir group ($P < 0.001$). Total cholesterol rose 53 mg/dL with d4T and 25 mg/dL with tenofovir ($P < 0.001$). The incidence of peripheral neuropathy also proved significantly higher in the d4T arm (7 versus 2 percent, $P < 0.001$).

HAART, the heart, and other muscles

Other Workshop studies looking at how HIV and its treatments affect the heart and other muscles offered greater challenges to clinicians a few years removed from physiology lectures. One study found a (possible) deficit with treatment, one a (possible) benefit, and one (possibly) neither.

Let's start with arteriovenous oxygen difference (a-vO₂) which, all will recall, measures the gap between how much oxygen the heart pumps out in refreshed blood and how much oxygen downstream muscles can suck up. To measure a-vO₂ rates and cardiovascular function, Todd Cade (University of Maryland, Baltimore) recruited 45 people, yoked them to the requisite sensors, and worked them on treadmills "to exhaustion" [abstract 16, L10]. Then he compared results in these 15 HAART-treated people, 15 untreated HIV-infected people, and 15 healthy controls matched for age, gender, and activity level. Although cardiac output and stroke rate proved equivalent in the three groups, the HAART group scored worst in a-vO₂ and peak heart rate (Table 4).

Among people on HAART, three more were taking an NNRTI than a PI, but that did not affect results in this small sample. Neither did race. Cade believes the results implicate HAART rather than HIV itself as the prime culprit in oxygen extraction by peripheral muscles, a deficit that may be mediated by NRTI-induced failings in

mitochondrial function. He noted, though, that he did not match the groups for lean mass, which can affect oxygen extraction. But no one in the study exercised enough to avoid the “sedentary lifestyle” label. Michael Dubé suggested that Cade’s findings may reflect the relative health of the three groups rather than antiretroviral therapy per se. The HAART group, he conjectured, may have been sicker than the untreated and healthy controls, and antiretrovirals may have improved their oxygen-extracting prowess. Although Cade could not rule out that possibility, he noted that no one in the study had a CD4⁺ nadir below 200 cells/mm³.

A noncomparative study by Kevin Yarasheski (Washington University, St. Louis) found that treatment-induced drops in viral load do help muscles in one way—by improving their ability to metabolize amino acids [abstract 18, L11]. His analysis of 10 men and one woman starting antiretroviral therapy suggested that every 10,000-copy drop in viral load allowed muscles to synthesize an extra 3 g of protein daily. The group’s baseline CD4⁺ count of 94 cells/mm³ climbed to 137 cells/mm³ with treatment ($P = 0.021$), while the median viral load nosedived from 171,758 copies/mL to 87 copies/mL ($P = 0.002$). During an average 4.3 months of treatment, mixed muscle protein synthesis rose from 16 to 20 percent daily ($P = 0.012$), still below the healthy norm of 25 percent. Plasma glutamine efflux, another measure of muscle moxie, improved significantly with treatment. Nine of the study participants were starting a salvage regimen, and two were starting their first antiretrovirals. Yarasheski recorded modest, nonsignificant gains in body muscle mass and thigh strength.

Even in people with marked peripheral atrophy, Giorgos Sakkas (University of California, San Francisco) found, muscle strength and intramuscular energy metabolism were not compromised [abstract 19, L12]. This small study compared six men with clinical and MRI evidence of severe atrophy and six HIV-infected men without atrophy. The atrophy group was significantly older (48 versus 37 years, $P = 0.02$), but the groups didn’t differ in body mass index, CD4⁺ count, duration of HIV infection, or current PI or NNRTI use. Nor did they differ in strength (maximum voluntary contraction) of the tibialis anterior muscle (which moves the foot up and

down). Several measures of mitochondrial function did not differ between groups.

The results suggest that mitochondrial depletion or damage recorded in people with lipoatrophy doesn’t hurt muscles. But the study has limits, Sakkas observed. First, the sample is small. Statisticians told Sakkas he would need 120 volunteers to show statistically significant differences in a study like this. Second, measuring muscle function at rest, as he did, doesn’t exclude the possibility that muscles of people with lipoatrophy come up short during exercise. Finally, the study did not compare the atrophic men with healthy volunteers.

HARD CHOICES

Management of antiretroviral-induced toxicities looks less bleak than it did only a few years ago. But even with more options on the table, the choices are still hard.

Swapping PIs for a nonnucleoside or abacavir can work as a fix for high lipids or insulin resistance, and more evidence shows that retiring d4T improves lactates and even fat atrophy. Yet switching is hardly risk free, as Graeme Moyle (Chelsea and Westminster Hospital, London) observes in a recent review.²⁰ The risk of losing viral control may not be great in people responding to their first PI regimen—a patient species on the wane. Risks are higher, maybe too high, in people with single- or dual-nucleoside experience before their PI. And the drugs replacing a PI (or d4T) have their own toxicities, which may be worse, in the short or long term, than the toxicity one hopes to reverse by switching. Finally, Moyle notes, open-label switch studies till a rich breeding ground for bias. Consent forms of randomized open-label trials pique concern about the toxicity of interest, and that may lead to faster dropouts or prompter reporting of side effects in non-switch arms.

Diet and exercise almost invariably yield morphologic and metabolic dividends, and two Workshop studies (reviewed below) show that both can be practical and cost effective. But they take guidance, time, and dedication, three items often in short supply among anxious people with an incurable disease.

Antilipid agents may ease antiretroviral-induced hyperlipidemia. But results of early statin studies have been inconsistent,

Table 5. **Subcutaneous fat gains (by DEXA) 48 weeks after switch from d4T**

New NRTI(s) (n)	Arms	Legs	Trunk
Abacavir (86)	37%	15%	19%
ZDV/3TC (32)	17%	7%	16%

Source: Grace McComsey, abstract H-1929.

and the statin that interacts least with antiretrovirals may be the weakest drug in the class.

Ironically, the side effect that seemed least treatable when the Lipodystrophy Workshop started four years ago, facial atrophy, has emerged as the one with potentially the most effective, least complicated, and most tolerable remedy. At least three surgical procedures are reversing facial atrophy, though they remain largely unavailable in some places, like the United States.

Switching from d4T for atrophy and high lactates

Before the Lipodystrophy Workshop and ICAAC, five studies—two of them randomized—showed that replacing d4T with ZDV, ZDV/3TC, or abacavir slowly but significantly reversed fat atrophy.²¹⁻²⁵ One of those studies updated 24-week data to 48 weeks at the two meetings, and a new case-control study logged increased fat trends after switching from d4T.

The noncomparative TARHEEL trial assigned 118 people with physically identified lipoatrophy, symptomatic lactates of 2.2 mmol/L or more, or lactates above 3.2 mmol/L to trade d4T for ZDV/3TC (as Combivir) or abacavir (if they had ZDV experience) [abstracts 21, L13; H-1929]. Grace McComsey reported that everyone had taken d4T for at least six months, and all had a viral load below 400 copies/mL on consecutive readings. Only 16 people in the study had high lactates, and they were more likely to be women (odds ratio 2.64) and African-American (odds ratio 4.50).

Eighty-six people switched to abacavir and 32 to Combivir. The tradeoff came with some risk. Five people had to stop because of hypersensitivity to abacavir, five stopped because of other side effects or clinical setbacks (pancreatic cancer, B-cell lymphoma, and bacteremia), and 14 others stopped returning for visits or left for “other” reasons. Only one person had a virologic breakthrough.

Table 6. Effects of good and poor adherence with a low-fat diet

	Adherence	Baseline (n =230)	Month 3 (n)	Month 6 (n)
Total cholesterol (mg/dL)	Good	282	235* (58)	253* (32)
	Poor	253	251 (103)	246 (38)
Triglycerides (mg/dL)	Good	345	280* (58)	240* (32)
	Poor	325	303 (103)	295 (38)
Body mass index (kg/m ²)	Good	24	23* (58)	22.4* (32)
	Poor	24	23.8 (103)	23.7 (38)

Source: Ana Barrios, abstract H-1929 and reference 26.

**P* < 0.05.

DEXA-measured subcutaneous fat in the arms, legs, and trunk grew in both switch groups, but more with abacavir (Table 5). Total CT-measured subcutaneous fat for both groups jumped by 23.5 cm² (*P* < 0.01), while visceral adipose tissue dipped by 2.8 cm². Most study participants (87 percent) gained subcutaneous fat by week 48, although about 60 percent claimed they saw no improvements in face, legs, arms, or buttocks on a body image questionnaire. Another 20 percent believed they gained “some” or “a lot” of fat, and the rest thought they lost fat. The liver enzyme aspartate aminotransferase (AST) fell from a median 40 U/L at baseline to 35 U/L at week 48, while alanine aminotransferase (ALT) dropped from 51 to 46 U/L. But not all lab values improved. Triglycerides rose from a median 244.5 mg/dL to 268.5 mg/dL at week 48.

A 12-month case-control study presented by Teresa García-Benayas (Carlos III Hospital, Madrid) compared 49 people who traded d4T for abacavir with 63 who continued d4T [abstract 57, L39]. Everyone had clinician-confirmed lipoatrophy, and no one changed their other antiretrovirals during follow-up. Skinfold measures showed a significant drop in triceps fat among the nonswitching controls, and nonsignificant drops in biceps, thigh, and calf fat. The people who switched to abacavir had nonsignificant fat gains in these four areas. Total body fat measured by bioelectrical impedance fell significantly over 12 months in the nonswitchers and rose slightly in the switchers.

Tracking lactate changes in the TARHEEL cohort, Tyler Lonergan (University of California, San Diego) found that levels stayed flat through 48 weeks in the 102 people who started the study with normal lactates and switched to abacavir or Combivir [abstract 21, L13]. The median lactate measured 2.9

mmol/L in the 16 people who started with high lactates. Ten of them stopped treatment until their lactates fell, and the median at the switch to abacavir or Combivir measured 2.1 mmol/L. After 48 months of abacavir or Combivir, the group’s median lactate level stood at 1.3 mmol/L.

In another study Lonergan showed that replacing withdrawn NRTIs in people with symptomatic high lactates usually does not kindle recurrent symptoms [abstract H-1080]. From 1998 through 2002, he tracked 12 people with one or more symptoms of hyperlactatemia (nausea/vomiting, abdominal pain, anorexia, weight loss, fatigue) plus at least two consecutive venous lactates twice the upper limit of normal (4.2 mmol/L in his lab). All 12 were taking d4T, six with 3TC, four with ddI, and two with abacavir. People stopped antiretrovirals until the lactates subsided, then five restarted regimens containing 3TC/abacavir, five ZDV/3TC/abacavir, and two ZDV/3TC. Two people stopped the rechallenge regimen for reasons unrelated to high lactates. One stopped because of recurrent symptoms. The other nine continued their new regimens for 127 to 1,161 days without recurrent symptoms. One of these nine had lactic acidosis before the NRTI switch.

Diet and exercise: those who can, win

One study explored diet and another exercise for lipid and weight abnormalities in people taking antiretrovirals. The diet study [abstract H-1929], involving 230 people with antiretroviral-induced dyslipidemia, appeared in print shortly after ICAAC.²⁶ Ana Barrios and colleagues (Carlos III Hospital, Madrid) made two important findings:

1. A six-month low-fat diet can significantly trim cholesterol, triglycerides, and body mass index.

2. Most people can’t stick with such a diet for even three months.

The Carlos III team enrolled people with cholesterol levels at or above 200 mg/dL (mean 257 mg/dL) or triglycerides at or above 200 mg/dL (mean 320 mg/dL). Two thirds had body fat abnormalities, and two thirds had a viral load below 50 copies/mL. About half were taking a PI regimen and half an NNRTI. No one switched antiretrovirals or started antilipid drugs during the study.

Only 161 people made it to the three-month mark, and only 36 percent of those reported good adherence with the low-fat diet. By month six only 70 people remained in the study, and 45 percent of them reported good adherence. Among people who stayed in the study and stuck with the diet, total cholesterol, triglycerides, and body mass index fell significantly (Table 6). People taking a PI started the study with much higher lipid levels, and enjoyed greater lipid improvements, than people taking an NNRTI. (The dietary delinquency in this study would not surprise Graeme Moyle, who noted during the Workshop that people he randomized to add pravastatin to a prescribed diet²⁷ stopped the diet when they started the drug.)

An exercise program thoughtfully planned by clinicians at New York’s Harlem Hospital Center met with the same success as the Carlos III diet: Most people could not keep to the program, but those who did reaped rewards. Led by Sai Subhasree Raghavan, the Harlem group got money from the city department of health for an exercise program that includes free membership at a fitness center one block from the hospital, exercise and nutrition evaluation and counseling, supervised twice-weekly training by a professional familiar with the local HIV community, and follow-up phone calls to encourage adherence [abstract 61, L41]. Despite these enticements, only 20 of 45 people with self-reported fat changes or weight gain enrolled in the program when invited, and only 10 exercised at least once weekly for eight weeks. Raghavan figured the cost per client at a thrifty \$33 per encounter hour.

The 16 men and four women who enrolled averaged 1.4 visits per week [abstract 60, L40]. They started with an average body mass index of 26.4 kg/m², 32.8 percent body fat, and a waist-to-hip ratio of 96. HDL-C, LDL-C, triglycerides,

Table 7. Antiretroviral and antilipid use in a managed care organization

	1998	1999	2000	2001
n	3,249	3,594	4,023	3,847
Antiretroviral use (%)	83.2	83.7	81.8	78.6
PI use (%)	70.4	67.8	60.7	54.6
Antilipid use in:				
PI treated (%)	8.7	12.6	14.3	18.4
Non-PI treated (%)	4.6	6.1	10.1	12.2
HAART naive (%)	2.2	2.4	5.5	5.5

Source: Uchenna Iloeje, abstract 42.

and glucose did not improve significantly over eight to 12 weeks, possibly because of the short duration. But study participants shed weight, mostly in subcutaneous fat. Skinfold measures showed significant improvements in triceps, biceps, thigh, abdomen, and subscapular and suprailiac areas. Hip circumference waned by 0.69 cm ($P = 0.004$), waist size by 1 cm ($P = 0.04$), and weight by three pounds ($P = 0.039$).

Options for facial atrophy

French researchers have chronicled successful treatment of facial atrophy with poly(lactic acid) (PLA, New-Fill) since the second Lipodystrophy Workshop. Now the first UK study—and the first randomized study anywhere—confirms these good results. Graeme Moyle randomized 30 people with facial atrophy to get PLA injections in the cheek and nasolabial regions immediately (at day one, week two, and week four) or later (at weeks 12, 14, and 16).

At week 12, ultrasound scans gauged a 4- to 5-mm increase in dermal thickness near the injection sites in the immediate-treatment group, but not in the delayed group. At week 24 the two groups had equivalent gains in dermal thickness. Before-and-after photographs evaluated by three clinicians not involved in the study confirmed these trends, with the best improvement seen in the lower buccal fat pad area. Moyle called the photo evaluation a “semiobjective” measure, and with good reason. The readers also noticed improvement in the temples, even though that area had not been treated. Moyle speculated that the improved cheek appearance “gives the assessor the impression of a generally ‘fuller’ face.”

The clinician panel did not rate the improved appearance as normal. Earlier studies suggest the need for four or five

PLA treatments to remedy the severe atrophy seen in the 28 men and two women who had three treatments so far in Moyle’s study. Only two people had treatment-related problems—a case of transient cellulitis that did not require antibiotics and delayed the next injection by one week, and superficial bruising that did not delay the next injection.

Although PLA injections remain the best-studied remedy for facial atrophy, not everyone in the field believes it’s the best. Derek Jones, a Los Angeles dermatologist who treats people with lipoatrophy, told the Workshop audience he has seen reversal of PLA’s effects within one year among people treated elsewhere. Parisian surgeon Patrick Amard, on the other hand, reports that he sees sustained improvement well beyond a year.²⁸ Jones favors a silicone microdroplet product called Silskin, which, unlike PLA, is available in the US. He claimed that migration of injected silicone has not been a problem with experienced practitioners. Migration, he said, results from injecting too much silicone in one session or using adulterated silicone. Jones and others plan a US trial of Silskin for people with HIV lipoatrophy.

A third technique involves collecting subcutaneous fat from a person’s abdomen, separating it from blood, and injecting it into the face. Drawbacks of this procedure compared with PLA injections include the need for hospitalization and a sufficient supply of abdominal fat. Parisian clinicians who tried fat implants in 12 men and three women excluded anyone with wasting or a CD4⁺ count below 100 cells/mm³.²⁹

An independent five-person panel, who reviewed before-and-after photos, and study participants themselves generally agreed on results six months after surgery. Thirteen of 15 patients felt they had good (9) or very good (4) atrophy correction,

while the panel gave good scores to 11 and a very good score to one. Eleven study participants thought they had good (7) or very good (4) global results, while panelists judged global results good in 11 and very good in two. MRI scans recorded an average six-month fat gain of 10.5 mm on the left side of the face and 10 mm on the right.

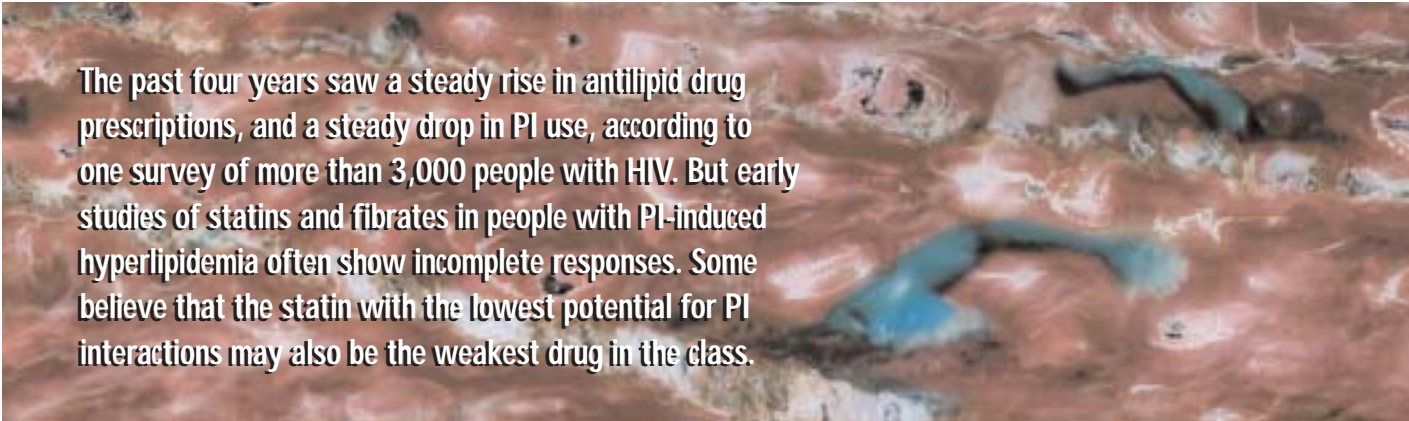
Alendronate for thin bones

A small randomized trial sized up the bisphosphonate alendronate in 22 men with osteoporosis or severe osteopenia [abstract H-1936]. Eugenia Negredo (Germans Trias i Pujol University Hospital, Barcelona) excluded people who had an antiretroviral treatment break within the preceding four weeks, a record of poor adherence, or secondary causes of osteopenia. She randomized 12 people to 10 mg of alendronate daily plus dietary counseling and 10 to counseling alone. The treatment group was older than the control group (46 versus 38 years), had a higher calcium intake (1,262 versus 1,040 mg/day), and smoked less (35 percent versus 55 percent).

After 24 weeks neither group had a significant change in bone mineral density. Three of 12 people taking alendronate improved from an osteoporosis ranking to osteopenia, while no one in the control group improved. At best the study suggests that, in a group like this, longer follow-up will be needed to see significant improvement in bone mineral density with alendronate.

Statins popular, but how potent?

HIV clinicians wondering how many of their colleagues use statins can stop wondering. Bristol-Myers Squibb did a time-trend analysis to find out, and the answer is “more and more.” Uchenna Iloeje and colleagues used electronic pharmacy, physician, and hospital claims from a US managed care organization to track antiretroviral and antilipid trends from 1998 through 2001 [abstract 42, L29]. The number of people with HIV in the organization remained fairly constant—between 3,000 and 4,000—over those years, but antiretroviral prescriptions dropped while antilipid prescriptions climbed (Table 7). Part of the jump in lipid-lowering therapy may reflect the aging of the cohort, because antilipid use also grew among HAART-naive people and among those taking non-PI regimens. In an analysis adjusted for



The past four years saw a steady rise in antilipid drug prescriptions, and a steady drop in PI use, according to one survey of more than 3,000 people with HIV. But early studies of statins and fibrates in people with PI-induced hyperlipidemia often show incomplete responses. Some believe that the statin with the lowest potential for PI interactions may also be the weakest drug in the class.

year, people taking a PI were 2.36 times more likely to be on lipid therapy than those not taking a PI.

About 90 percent of the people in this survey were men. In another study of 24,862 men and 8,735 women with HIV enrolled in California's Medi-Cal program between January 1996 and June 2000, Iloeje found that men taking PIs were three times more likely to get an antilipid prescription than women taking PIs [abstract 43, L30].

Are the lipid drugs working? Results so far are mixed. A few years ago a randomized trial by Graeme Moyle found that pravastatin (40 mg daily) plus dietary advice for 24 weeks lowered cholesterol (mostly LDL-C) more than dietary advice alone in 31 men who started with levels above 250 mg/dL.²⁷ But a study that randomized 170 people with high lipids to pravastatin (40 mg daily) or fenofibrate (200 mg daily) found that the drugs helped few people achieve NCEP lipid goals in 12 weeks.³⁰

At the Lipodystrophy Workshop a placebo-controlled trial of pravastatin in HIV-infected people with high lipids found an incomplete response to the drug [abstract 50, L34]. The results led James Sosman and coworkers (University of Wisconsin, Madison) to conclude that "combinations of lipid-lowering therapies may be needed to normalize the lipoprotein abnormalities observed in patients taking PIs."

The study included 15 men and one woman with triglycerides above 150 mg/dL, LDL-C above 130 mg/dL, and HDL-C below 40 mg/dL while taking a suppressive PI regimen for at least three months. After four weeks of good adherence with a low-fat, low-cholesterol diet, they continued the diet and took either pravastatin (40 mg daily) or placebo for eight weeks. Total

cholesterol, LDL-C, non-HDL-C, and triglycerides fell significantly with pravastatin but not with placebo. But pravastatin did not improve an atherogenic profile characterized by mildly elevated LDL-C particle concentration, decreased large HDL-C, and increased large VLDL-C (see Table 3). Sosman added that the "magnitude of improvement [in the main lipid measures] appears less than in clinical trials of HIV-negative patients."

In a Workshop review lecture, Peter Reiss (Academic Medical Center, Amsterdam) noted the irony that pravastatin interacts with PIs less than other statins, but it may be the weakest drug in the group.

So how about fluvastatin? Again, the drug fell short by some lipid measures in a placebo-controlled crossover trial published just after the Workshop.³¹ Fourteen men and two women with hyperlipidemia while taking a PI took fluvastatin (40 mg daily) or placebo for four weeks, then crossed over to placebo or fluvastatin after a two-week washout. Although triglycerides did not drop with treatment, total cholesterol fell from 8.0 mmol/L (309 mg/dL) to 6.6 mmol/L (255 mg/dL) ($P < 0.001$) and the total cholesterol-to-HDL-C ratio dropped from 7.3 to 6.4 ($P < 0.01$). But the authors write that "the amplitude of this lipid-lowering effect was limited" because eight of the 16 study participants still had cholesterol readings above 7.0 mmol/L (270 mg/dL) and triglycerides above 3.0 mmol/L (266 mg/dL) after finishing their course of fluvastatin, compared with 10 of 16 before treatment.

Other morsels of good news for people suffering PI side effects turned up in the literature around the time of the Lipodystrophy Workshop. Rosiglitazone improved glucose disposal and added subcutaneous fat in eight people with HIV infection and insulin resistance.³² Study

participants had a glucose disposal rate of 3.8 mg per kg of lean body mass per minute compared with 11.08 mg in healthy age- and weight-matched controls ($P < 0.001$). After six to 12 weeks of rosiglitazone at a dose of 8 mg daily, glucose disposal improved by 59 percent to 4.99 mg ($P = 0.02$). CT-measured subcutaneous adipose tissue rose by 23 percent ($P = 0.05$), and visceral adipose tissue dropped by 21 percent ($P = 0.04$). Rosiglitazone did not affect viral load or CD4⁺ count in study participants.

An earlier placebo-controlled trial of rosiglitazone at the same dose in 30 people with HIV lipodystrophy found improved insulin levels.³³ In this study subcutaneous peripheral fat, visceral fat, and waist-to-hip ratio did not improve significantly with rosiglitazone, but the trial was powered to detect only substantial fat changes. A large study of rosiglitazone in people with HIV infection is under way in Australia.

APPENDIX A. Appendix

This is not really an appendix; it's really about the appendix. Daniel Klein, the clinician whose digital delvings into the Kaiser Permanente health care system database furthered the understanding of antiretrovirals and heart disease,¹³ has turned his attention to the intestinal cul-de-sac that does nothing but cause trouble [abstract H-1154]. He found that it causes trouble more often in men with HIV than in men without HIV.

Comparing 6,436 HIV-infected men with 18,438 uninfected men, Klein calculated a crude appendicitis rate of 3.3 hospital admissions per 1,000 person-years in the HIV group versus 0.86 in the non-HIV group. Adjusted for age, the relative rates measured 2.9 with HIV and 0.92 without

HIV ($P < 0.001$). Because rates in men with HIV did not increase from 1991 to 2001, it appears that the more potent HIV therapies used since 1996 did not worsen the incidence of appendicitis seen with earlier regimens. Klein charted use of one or more PIs in 66 percent of HIV-infected men without appendicitis and in 72 percent of those with appendicitis, a nonsignificant difference. Nor did CD4⁺ count, duration of HIV infection, or immune reconstitution appear to influence rates of appendicitis. But because a higher proportion of men with than without appendicitis were taking some antiretroviral (81 percent versus 65 percent, $P < 0.05$), Klein proposed that “the role of [antiretroviral] use in general needs further study.”

Since 1996, hospital stays for appendicitis lasted no longer in HIV-infected men than in uninfected men. The HIV group had a higher percentage of perforations than the non-HIV group (27 percent versus 16 percent), but that difference lacked statistical significance. A lower CD4⁺ count did not predict perforation. In the HAART era men with HIV and appendicitis were much less likely than uninfected men to have a white blood cell (WBC) count above $12.5 \times 10^3/\mu\text{L}$ upon admission to the hospital (26 percent versus 70 percent, $P < 0.001$). Klein concluded that “clinicians should be quick to consider appendicitis when presented with right lower quadrant pain in HIV-infected patients but should not rely on elevated WBCs in making a diagnosis.”

APPENDIX B. Bone

Daniel Klein’s data-packed poster (see Appendix A) reminds us again that sheer clinical number crunching can offer ready insights into clinical practice. But, as he observes, this revealing inquest does not explain *why* appendicitis appears to favor people with HIV. This need to know the *why’s* is one thing that keeps bench scientists on the payroll in academia and industry. Thanks to some of them, the cellular nuts and bolts of HIV lipodystrophy and other toxicities are finding their way to the right bins in the pathogenic toolbox.

That’s why it’s important to tough through those slide talks on 3T3-F44A2 cells, as a largely clinical audience did at the 4th Lipodystrophy Workshop. You never know how close that bench will get to your bedside. Take, for example, a

study of 3T3-F44A2 cells by Rik Derynck and colleagues in the School of Dentistry at the University of California, San Francisco.³⁴ Derynck found that he could take these undifferentiated fat cells, or pre-adipocytes, juice them with a little retinoic acid and something called bone morphogenetic protein, and radically change their destiny. Instead of becoming fat, the 3T3-F44A2s became bone.

By tinkering with these cells’ signaling systems, Derynck said, “one can do things that one has not thought of before. In effect, the life of these fat cells has been changed from fat to bone. Now we can begin to think about therapeutic applications.”³⁵

HIV docs can think of one. ■

Mark Mascolini writes about HIV infection (mailto:mailmark@ptd.net).

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ABSTRACTS

Editor's Note: Following are select abstracts from the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held September 27-30, 2002, in San Diego, California. Look to the December 2002 issue of the IAPAC Monthly for 42nd ICAAC coverage by writer-at-large Mark Mascolini.

Comparable antiviral efficacy and safety of lamivudine administered 300mg once-daily (QD) versus 150mg BID both in combination with zidovudine (300mg BID) and efavirenz (600mg QD) in HIV-1-infected, antiretroviral-naive adults

E DeJesus, B Grinsztejn, K Gough, et al.

Background: The current approved dose of lamivudine (3TC) for the treatment of HIV infection is 150 mg twice daily (BID), however, the pharmacokinetic profile suggests that it may be successfully dosed once daily (QD). This study was designed to evaluate the efficacy and safety of a simplified dosing formulation of 3TC (300 mg QD) compared to the standard dose of 150 mg BID, both in combination with zidovudine (ZDV 150 mg BID) and efavirenz (EFV 600 mg QD). **Methods:** The primary objectives of this randomized, double-blinded, placebo controlled study were to compare the magnitude of viral suppression by quantitation of plasma HIV-1 RNA (vRNA levels) (≤ 400 copies/mL and ≤ 50 copies/mL), and immunological response measuring absolute CD4 cell counts.

Results:

Population ITT, M=F	vRNA ≤ 400 copies/mL at week 48	vRNA ≤ 50 copies/mL at week 48	Median Δ CD4 cells/mm ³ at week 48
3TC QD	178/278 64%	165/278 59%	144
3TC BID	174/276 63%	168/276 61%	146

Only eight subjects experienced an SAE attributed to study drug (QD: three; BID: five). There were no deaths during this study and more patients prematurely discontinued study drug due to an AE in the BID group than the QD group (QD: 7%; BID: 13%). The most commonly reported AEs were nausea, dizziness and fatigue. **Conclusion:** These data suggest that the use of 3TC QD as a component of a triple drug regimen is as effective as 3TC BID. Both dosing regimens were well tolerated with no new or unexpected safety concerns.

Abstract H-161

Lopinavir/ritonavir (Kaletra) in antiretroviral-naive HIV+ patients: 4-year follow-up

R Murphy, S Brun, M King, et al.

Background: Kaletra is a coformulation of lopinavir (LPV), an HIV protease inhibitor (PI), and ritonavir (r), a CYP3A inhibitor, providing increased plasma levels of LPV. Clinical trials of LPV/r are ongoing in HIV infected patient populations. Data on long-term outcomes are limited. **Methods:** In the longest prospectively followed group of patients treated with LPV/r, 100 antiretroviral (ARV)-naive patients received d4T/3TC and one of three doses of LPV/r. After 48 weeks, patients began open-label treatment with LPV/r 400/100 mg BID with continued follow-up every three months. **Results:** Median baseline (BL) HIV RNA was 4.9 log₁₀ copies/mL and median BL CD4 count was 338 cells/mm³. Prior to week 192, 28/100 patients discontinued study therapy due to adverse event (AE, seven attributed to LPV/r therapy, three unrelated to LPV/r), lost to follow-up (eight), noncompliance (four), and other reasons (six). HIV RNA was < 400 copies/mL in all 72 patients (72%, ITT missing = failure) continuing on study at week 192; among patients who have reached week 204 to date, 46/47 had HIV RNA < 400 copies/mL and 45/47 had HIV RNA < 50 copies/mL. The remaining 25 patients continue on study but have not yet reached week 204. CD4 counts increased consistently throughout the study period; the mean increase from baseline to week 192 was 416

cells/mm³. The most common drug-related AEs of at least moderate severity were diarrhea, nausea, and abdominal pain. Data will be presented through week 204 on all 100 patients enrolled. **Conclusions:** LPV/r-based therapy demonstrated sustained antiviral activity and was generally well tolerated in ARV-naive patients through four years of therapy.

Abstract H-165

Enfuvirtide (T-20) in combination with an Optimized Background (OB) regimen versus OB alone: Week 24 response among categories of treatment experience and baseline (BL) HIV antiretroviral (ARV) resistance

JP Lalezari, K Henry, M O'Hearn, et al.

Background: TORO 1 (T-20 versus Optimized Regimen Only) is a Phase III study of enfuvirtide, the first fusion inhibitor which targets HIV gp41, inhibiting viral fusion to host cells. **Methods:** Patients with ≥ 6 months prior experience with three classes of ARVs, and HIV-1 RNA $\geq 5,000$ copies/mL selected an OB regimen of three to five ARVs based on prior history and BL genotypic (GT) and phenotypic (PT) viral resistance. Patients were randomized 2:1 to enfuvirtide (90 mg SC BID) + OB or OB alone. **Results:** The primary 24-week analysis contained 491 patients. Median BL HIV-1 RNA was 5.2 log₁₀ copies/mL, and CD4 count 80 cells/mm³. 54% of patients had CD4 counts < 100 cells/mm³ and 61% of patients had HIV RNA $> 100,000$ copies/mL. 69% of BL viral isolates from patients had PT sensitivity to ≤ 2 ARVs, and 68% of viral isolates had HIV GT sensitivity to ≤ 2 ARVs. Least squared means of change from BL in viral load (ITT, Last Observation Carried Forward) was -1.697 log₁₀ copies/mL for T-20 + OB, and -0.763 log₁₀ copies/mL for OB alone, a delta of 0.934 log₁₀ copies/mL ($p < 0.0001$). Further analyses according to BL demographics, ARV experience, and HIV resistance indicated that treatment with T-20 provided consistently better HIV RNA suppression. Aside from injection site reactions, which required discontinuation in $< 3\%$ of patients, safety was comparable between treatment groups. **Conclusions:** Enfuvirtide added to OB provided additional viral suppression compared to OB alone in highly ARV-experienced patients as well as among a variety of sub-groups based on BL characteristics.

Abstract H-1074

Salvage therapy with lopinavir/ritonavir (LPV/r), amprenavir (APV) \pm an additional boost with ritonavir (RTV) in HIV-infected patients with multiple treatment failure: Final 26-week results of Puzzle 1-ANRS104 Study

G Raguin, G Chene, L Morand-Joubert, et al.

Background: A combination of APV, LPV and RTV could prove effective in patients having failed multiple antiretrovirals provided that pharmacokinetic interactions between APV and LPV have no negative effect on virologic response. **Methods:** A prospective, randomized, open-label, multicenter trial in patients with CD4 count 10,000 copies/ml after at least two PIs and one NNRTI. All patients were treated with LPV/r + APV and were randomized to receive or not an additional boost of 200 mg RTV. **Results:** 40 patients were randomized, 37 started treatment. At baseline, median CD4 was 207 cells/mm³, median pVL 4.7 log₁₀ copies/ml, median number of baseline PI mutations: seven, median phenotypic resistance index: 9.7 for LPV and 2.6 for APV. Average number of antiretrovirals taken prior to randomization was 7.7. Median pVL (log₁₀ copies/mL) changes at week 26 were significantly larger in patients with the additional boost of RTV (400 mg/d; n=18): -2.5 than in those with 200 mg/d RTV (n=19): -1.4 ($p = 0.02$). 61% (11/18) reached a pVL < 50 copies/ml versus 32% (6/19), respectively ($p = 0.07$). Treatment discontinuation occurred in four patients in each group and grade IV adverse events in six patients in each group. After adjustment for RTV group, a lower

number of baseline PI mutations was associated with a lower pVL at week 26. Baseline phenotypic resistance index was not predictive of virologic response. **Conclusions:** In patients having failed multiple antiretrovirals, a combination of APV, LPV/r with an additional boost of RTV shows a significant virologic response despite a pharmacokinetic interaction between LPV and APV previously documented in this study.

Abstract H-1078

Atazanavir (ATV) QD and efavirenz (EFV) QD with fixed-dose ZDV+3TC: Comparison of antiviral efficacy and safety through week 24

KE Squires, A Thiry, M Giordano (for the AI424-034 International Study Team)

Background: ATV is a potent, safe, once-daily protease inhibitor that has a favorable resistance profile, rapidly suppresses HIV RNA, increases CD4 cells and provides superior lipid profile to other PIs. EFV, a potent, once-daily NNRTI, is a standard of care in antiretroviral (ARV)-naïve patients. **Objectives:** Compare antiviral efficacy, safety of ATV and EFV through week 24; percentage of subjects with HIV RNA levels <400 and <50 copies/mL; mean changes from baseline in CD4 and fasting LDL cholesterol and triglycerides (TG). **Methods:** Double-blind, multinational, randomized (1:1) trial in ARV-naïve subjects receiving ATV (400 mg QD) or EFV (600 mg QD) each with fixed-dose ZDV+3TC. **Results:** Baseline status for ATV, EFV, respectively: treated n=404, 401; men 64%, 66%; mean HIV RNA 4.86, 4.82 log₁₀ copies/mL; mean CD4 314, 330 cells/mm³. The efficacy and lipid results at week 24 are depicted in the following table:

< 400 copies/mL ¹	< 50 copies/mL ¹	Δ CD4	% Δ LDL-C	% Δ TG	
ATV	72% (291/401)	26% (106/404)	+129	+1%	-11%
EFV	69% (278/401)	31% (126/401)	+106	+18%	+16%
Comparison	95% CI= (-3.5%, 9.0%) ²	95% CI= (-11.2%, 1.0%) ²	p<0.0001 ³	p<0.0001	p<0.0001

¹ ITT (NC=F) Discontinuations, CDC Class C AIDS, confirmed rebound after response = failure.

² Met objective showing similarity (lower 95% CI limit > -12%).

³ Time-averaged difference (ATV - EFV) through week 24.

Safety: Discontinued (% subjects) up to week 24 (due to AE): ATV 8 (5), EFV 15 (7). CNS, rash were more frequent with EFV; jaundice including scleral icterus was more frequent with ATV. **Conclusions:** ATV once daily has similar antiviral efficacy to a standard of care regimen with EFV through 24 weeks. Both were safe, well tolerated. ATV was associated with decreases or minimal increases in lipid parameters.

Abstract H-1076

Drug-drug interaction study with intravenous cidofovir (CDV) and either trimethoprim/sulfamethoxazole (TMP/SMX), didanosine (ddI), or fluconazole (FLU) in HIV-infected individuals

A Luber, J Lalezari, J Rooney, et al.

Background: CDV coadministered with high dose probenecid (PRB) could potentially interact with agents sharing a renal elimination pathway. TMP/SMX, ddI, and FLU are commonly used in HIV-infected patients and are eliminated renally to a substantial degree. **Methods:** HIV-positive males (n=18) were assigned to three groups (n=six each) in a multiple-dose, sequential, open-label design wherein patients received CDV 3 mg/kg IV over one hour (with saline and PRB) on day 1 and day 8 and either TMP/SMX one double strength tablet/day or ddI 200 mg BID (100 mg BID if <60 kg) on days 2 through 8, or CDV on days 1 and 14 with FLU 100 mg/day on days 2 through 14. Serial blood and urine were collected over 24 hours and pharmacokinetic parameters were calculated by noncompartmental methods for CDV on days 1, 8, and 14 (FLU group); for TMP/SMX and ddI on days 7 and 8, and for FLU on days 13 and 14. Pharmacokinetic parameters for each agent given alone versus with cidofovir were compared using the Wilcoxon signed-rank test. Safety was assessed by serial clinical and laboratory assessments. **Results:** Coadministration with TMP/SMX, ddI, or FLU had no effect on the pharmacokinetics of CDV. FLU's pharmacokinetics were not affected when given with CDV/PRB. Exposures (AUC, C_{max}) of both TMP and SMX were decreased by approximately 30% and CL/F and CL_{renal} were significantly increased (p=0.03) in the presence of CDV/PRB. The AUC of ddI was increased 1.6 fold when coadministered with CDV/PRB versus administration alone (2,166 ± 795 versus 1,298 ± 414 mg·hr/mL; p=0.03). One patient experienced a severe headache while another experienced lightheadedness on

two occasions. **Conclusions:** CDV's pharmacokinetics are not significantly affected by coadministration with TMP/SMX, ddI, or FLU. Given the infrequent dosing schedule of CDV/PRB (q week - q o week), alterations in the pharmacokinetics of TMP/SMX and ddI are unlikely to be of clinical relevance and do not warrant alterations in dosing of these agents.

Abstract A-1828

Pravastatin, atorvastatin, bezafibrate, and fenofibrate in the treatment of highly active antiretroviral therapy-associated hyperlipidemia in HIV-infected patients

L Calza, R Manfredi, F Chiodo

Background: Frequent elevations in plasma lipid levels have been reported in association with protease inhibitor (PI)-based highly active antiretroviral therapy (HAART), and prolonged metabolic imbalances could significantly act on the long-term prognosis and outcome of HIV-infected individuals. **Methods:** 93 patients on PI-based HAART since at least 12 months and presenting hypertriglyceridemia (>300 mg/dL), with or without hypercholesterolemia (>280 mg/dL) and lipodystrophy, of at least six months duration and unresponsive to a hypolipidemic diet and physical exercise have been treated with fibrates or statins for 12 months. 27 patients received bezafibrate (400 mg daily), 25 fenofibrate (200 mg), 22 pravastatin (20 mg), and 19 atorvastatin (20 mg). **Results:** Six patients were excluded from evaluation due to early drop out. At the close of one-year follow-up, fibrates led to a reduction of 40.1% and 28.7% versus baseline triglyceride and total cholesterol levels, respectively (p<0.001); no significant difference of hypolipidemic therapeutic response was detected according to different administered fibrates. After the same 12-month study period, statins led to a reduction of 38.9% and 30.4% versus baseline triglyceridemia and cholesterolemia, respectively (p<0.001), without significant difference between pravastatin and atorvastatin. Mild gastroenteric symptoms were found in only eight (9.1%) of the 87 treated patients, while a transaminase elevation was described in only two (2.3%) subjects. **Conclusions:** In our study, pharmacological treatment with bezafibrate, fenofibrate, pravastatin, or atorvastatin proved certainly effective in the management of diet-resistant HAART-associated dyslipidemia, with a favorable tolerability profile. Particularly, no significant difference of therapeutic response was observed according to different classes of employed hypolipidemic agents.

Abstract H-1932

Favorable lipid and mitochondrial (mt) DNA profile for tenofovir disoproxil fumarate (TDF) compared to stavudine (d4T) in combination with lamivudine (3TC) and efavirenz (EFV) in antiretroviral therapy (ART) naïve patients: A 48-week interim analysis

J Gallant, S Staszewski, et al.

Background: TDF is a single tablet, once-daily nucleotide analog reverse transcriptase inhibitor with *in vitro* data demonstrating lack of mt toxicity as determined by mt DNA content and lactic acid production. **Methods:** Ongoing 3-year phase III multicenter randomized double blind active controlled trial in ART-naïve patients who received EFV and 3TC bid plus either TDF qd or d4T bid with d4T placebo bid or TDF placebo qd. **Results:** The intent-to-treat (ITT) population (n=600) had a mean age of 36 years; 24% were female; mean HIV RNA was 4.9 log₁₀ copies/mL; mean CD4 count was 279 cells/mm³. In the ITT missing = failure analysis, 87% patients in both arms achieved HIV RNA <400 copies/mL. HIV RNA was <50 copies/mL in 82% and 81% of the TDF and d4T arms, respectively. A mean increase from baseline of 169 and 167 CD4 cells was observed in the TDF and d4T groups. The incidence of grade 3/4 adverse events (19% and 17%) and lab abnormalities (28% and 31%) were similar in the TDF and d4T groups. A significant mean increase from baseline in triglyceride levels (74 versus 0 mg/dL, p<0.001) was seen in the d4T compared to the TDF arm. Mean increases in total cholesterol in the d4T and TDF arms were 53 and 25 mg/dL, respectively (p<0.001). The incidence of nucleoside associated toxicities (lactic acidosis, peripheral neuropathy, lipodystrophy) in the TDF arm was 3% compared to 10% in the d4T arm (p<0.001). Notably, in a substudy analysis (n=227) the median increase from baseline in mt DNA copies/cell was 82 in the TDF arm versus 18 in the d4T arm (p=0.001). **Conclusions:** Through 48 weeks, TDF/EFV/3TC was highly efficacious and comparable to d4T/EFV/3TC. Patients in the TDF arm had a favorable lipid and mt DNA profile with fewer nucleoside-associated adverse events.

Abstract LB-2



I N T H E L I F E



Steven C. Zell

Vanity Fair readers have every month since 1993 enjoyed *The Proust Questionnaire*, a series of questions posed to celebrities and other famous subjects. In May 2002, *IAPAC Monthly* introduced "In the Life," through which IAPAC members are asked to bare their souls by answering 10 questions.

This month, *IAPAC Monthly* is proud to feature Steven C. Zell, who is Professor of Medicine at the University of Nevada, School of Medicine in Reno, Nevada.

What proverb, colloquial expression, or quote best describes how you view the world and yourself in it?

"I don't want to achieve immortality through my work; I want to achieve it through not dying!" –Woody Allen

What activities, avocations or hobbies interest you? Do you have a hidden talent?

I am blessed living in the Lake Tahoe, Nevada, region with unlimited access to outdoor activities. Summers are spent backpacking, hiking, fishing and road bicycle touring. Winters I spend cross-country skiing, with an occasional snowshoe trek. My hidden talent rests in my ability to detail automobiles to a "like new" state.

If you could live anywhere in the world, where would it be?

New Zealand would be my choice simply because it combines the best balance of people living sparsely in harmony with an abundance of natural beauty.

Who are your mentors or real life heroes?

Magic Johnson is my real life hero as he has always displayed an enthusiasm towards his work unparalleled by others. His courage to come forth with his HIV infection and step out of NBA basketball is a sacrifice that is beyond words.

With what historical figure do you most identify?

I've always felt a kinship to John Muir as I am a lover of the Sierra Nevada Mountains and share his sense of duty to protect this cathedral of nature for future children.

Who are your favorite authors, painters, and/or composers?

Author: Tom Clancy; Painter: None, but my favorite photographer is Ansel Adams; Composers: John Lennon and Paul McCartney of the Beatles.

If you could have chosen to live during any time period in human history, which would it be?

I suspect being alive in the late 1800s would have been fascinating, especially if one were involved in the exploration and colonization of the great Western United States.

If you did not have the option of becoming a physician, what would have you likely become given the opportunity?

I certainly would have become involved in teaching as the highlights and directions of my life have always revolved around education. I could see myself as a high school science teacher and an after-school basketball coach.

In your opinion, what are the great achievements and failures of humanity?

The greatest achievement of humanity has been the international cooperative effort in research and development of modern medical technology. The greatest failure is our inability to deliver such technology to the world's population in an equitable fashion.

What is your prediction as to the future of our planet one full decade from present day?

My intuition is that the world will continue to spiral in aggression as those separated by faith and culture grow farther apart. My hope is that evolutionary forces will find that peace is a more productive state for the world to trend towards than hatred and bigotry. ■



[Strength in Numbers]

[IAPAC Welcomes New and Renewing Members]

In October 2002, the International Association of Physicians in AIDS Care (IAPAC) welcomed 73 new and renewing dues-paying members from 11 countries. IAPAC thanks the following physicians and allied health workers for their support of the association's mission to improve the quality of care provided to men, women, and children who are living with HIV/AIDS.

Kathryn Anastos, *USA*
Felipe M. Azonzo-Vazquea, *Mexico*
Joseph Beck, *USA*
Margarita R. Cancio, *USA*
Carlos José Castro-Sansores, *Mexico*
Adolfo Palma Chan, *Mexico*
E. Griffin Cipolla, *USA*
Robert W. Clausen, *USA*
Carlos A. Cohen, *USA*
Bob Colebunders, *Belgium*
Ann Dreyer, *USA*
Ronald W. Falcon, *USA*
Martin Fenstersheib, *USA*
David J. Gaber-Osorno, *Mexico*
Renan Alberto Gongora-Biachi, *Mexico*
Pedro Gonzalez-Martinez, *Mexico*
Margaret J. Gorensek, *USA*
Cyril Goshima, *USA*
Frank Graziano, *USA*
Alejandro Guerrero, *Mexico*
Roberto Gutierrez Gonzalez, *Costa Rica*
Linda Haberman, *USA*
Scott G. Hartman, *USA*
Philippe L-A Henrivaux, *Belgium*

David Herman, *USA*
Mark Higgins, *USA*
Asim Jani, *USA*
Joseph Jemsek, *USA*
Donald Kaminsky, *USA*
Donald Kilby, *Canada*
John Lambert, *UK*
Dora M. Lara-Perera, *Mexico*
James T. Lee, *USA*
Anthony Lee, *USA*
Marah J. Lee, *USA*
Theodore H. Lenox, *USA*
Paul Lorenson, *USA*
Janet McDermott, *USA*
Anthony Milanes, *USA*
Donna Mildvan, *USA*
Cynthia Miller, *USA*
Flavia Jastine Mugala, *Namibia*
Robert J. Munk, *USA*
Esther Mwaikambo, *Tanzania*
Raymond Noel, *USA*
Edward C. Oldfield III, *USA*
Norma R. Pavia-Ruz, *Mexico*
Barbara Lee Perlmutter, *USA*
Kevin L. Peterson, *USA*
Janice Piatt, *USA*
Timothy Poirier, *USA*
John Post, *USA*
José Prieto, *USA*
Ramon Ramirez, *USA*
Steven I. Rapaport, *USA*
Kristen Ries, *USA*
Russel Amir Rodriguez, *Mexico*
Neal Rzepkowski, *USA*

Adrian Rivero Santos, *Mexico*
Vijayesvara Sarma, *India*
Gisela Schneider, *Gambia*
Sheetal Sharma, *USA*
Bary Siegel, *USA*
Colette Simon, *USA*
Tin Soe, *Marshall Islands*
Raul A. Sosa, *Mexico*
Lisa L. Stocking, *Botswana*
Daniel Toub, *USA*
Ligia C. Vera-Gamboia, *Mexico*
Keith Vrhel, *USA*
Ned Brian Westveer, *USA*
Benjamin Young, *USA*
Steven C. Zell, *USA*

Also in October 2002, the following institutions renewed their institutional memberships: the CDC-NCHSTP Information Center; IMS Health; National Hemophilia Foundation; and Philadelphia Fight. And, Merck & Co. renewed its IAPAC Corporate Partner status. In addition to supporting ongoing activities, Merck & Co.'s Corporate Partner contribution will subsidize IAPAC professional memberships for five developing world physicians.

To learn more about professional and institutional memberships, call (312) 795-4934 or send an e-mail to member@iapac.org. For information regarding Corporate Partner opportunities, call (312) 795-4941 or send an e-mail to partner@iapac.org.

[Recruit your colleagues to join IAPAC]

Health professionals who join the International Association of Physicians in AIDS Care (IAPAC) benefit from the research and expertise disseminated through the association's journals, Web site, care tools, and annual symposia. Greater membership in IAPAC also means more support for the association's training programs. These programs are making great strides in helping professionals learn best practice care techniques in the developing world, where the pandemic is taking its heaviest toll. Finally, as IAPAC continues to find strength in numbers, and represent more and more of the

world's health professionals, expanded membership means a more powerful voice in discussions that can lead to increased funding for medications, more effective inter-organizational cooperation, and simply better quality of life for those living with HIV disease.

These reasons should be more than enough to encourage you to recruit colleagues to join IAPAC. Nonetheless, we want to provide you with personal rewards for your recruitment efforts.

Through the end of 2002, every new recruit who lists you as the member who referred him/her to IAPAC brings you

closer to winning free travel and/or a complimentary membership extension. For each member you recruit, your name will be entered in a drawing for one roundtrip airline ticket within your continent or region of the world. If you recruit five new members before the end of the year, you will receive 12 months of dues-free membership.

Battling complacency and advancing commitment in the international struggle against HIV/AIDS requires a strong, coordinated effort. Encourage your colleagues to join that effort as members of IAPAC.

IAPAC survey finds strong link between HIV and mental health

Key findings of a national physician and patient survey conducted by the International Association of Physicians in AIDS Care (IAPAC) in the United States demonstrate a strong link between HIV infection and the mental health of patients diagnosed with HIV disease. According to physician respondents, more than 80 percent of their HIV-positive patients suffer from symptoms of depression or anxiety. Although psychiatric symptoms in patients with HIV infection have a variety of causes, including the direct central nervous system (CNS) effects of HIV, CNS opportunistic infections, and street drugs, the majority of surveyed physicians also believe that HIV medications (antiretroviral drugs) are a leading cause of their patients' most common mental health symptoms (83.6 percent).

The results of the survey, which queried more than 130 HIV-treating physicians and 235 HIV-positive men and women, were presented during an October 26, 2002, IAPAC press conference held in conjunction with the 40th Annual Meeting of the Infectious Disease Society of America (IDSA).

"These data clearly demonstrate that physicians must take seriously the psychiatric condition of their HIV-positive patients," said Ewald Horwath, Associate Clinical Professor of Psychiatry at the College of Physicians and Surgeons of Columbia University. "As physicians, we must more aggressively evaluate HIV-positive patients for psychiatric symptoms. This may require a medical work-up to rule out CNS opportunistic diseases, cognitive



Ewald Horwath

evaluation to rule out HIV-associated dementia, review of antiretroviral regimens for agents that cause CNS side effects, and referral for psychiatric consultation." Horwath, who analyzed the survey results, has authored a supplement to IAPAC's quarterly scientific peer-reviewed journal, *JIAPAC*, which focuses on psychiatric manifestations of HIV infection, incorporating key data from the survey.

More than 80 percent (84.3 percent) of physician respondents said that their HIV-positive patients frequently or very frequently suffered from symptoms of depression. Anxiety (81.4 percent), headaches (74.6 percent), lethargy (72.3

percent), and insomnia (71.5 percent) were highlighted as the most common symptoms in HIV-positive patients according to their physicians.

Patients being treated for HIV corroborated the physicians' findings with regard to common symptoms experienced, with 72 percent experiencing depression and 65 percent experiencing anxiety. Lethargy (43 percent), irritability (41 percent), impaired concentration (40 percent), and mood swings (40 percent) were also leading symptoms experienced by patients.

To treat these symptoms, physicians most frequently prescribed antidepressant drugs (79.6 percent) to patients and also recommended that patients switch from their current antiretroviral regimens (56.6 percent), where specific antiretroviral agents may be responsible.

Physician and patient survey questionnaires were developed by IAPAC in coordination with Horwath. IAPAC gathered physician responses through 15-minute telephone interviews and signed fax-back response sheets, conducted with a segment of its US physician members. IAPAC contracted Wirthlin Worldwide to field the patient questionnaire via an online survey hosted on www.thebody.com. Funding for the survey was provided by an educational grant from Boehringer Ingelheim Pharmaceuticals, Inc.

To obtain a copy of the *JIAPAC* supplement, "Psychiatric and Neuropsychiatric Manifestations of HIV Infection," visit the Order Publications section of the IAPAC Web site—www.iapac.org. ■



SAY ANYTHING

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No one diminishes the question of security. God knows, in this day and age it's a consuming obsession. But it does say something about the way we respond to the human condition, doesn't it? It's not enough to engage the world simply by having an incomparable human catastrophe; it has to have security implications to make it come alive.

Stephen Lewis, UN Special Envoy for HIV/AIDS in Africa, during a speech to conferees at the US Center for Strategic and International Studies who gathered October 4, 2002, to discuss "States Threatened by the Second Wave of HIV/AIDS: China, India, Nigeria, Russia, and Ethiopia." The conference was inspired by a report from the National Intelligence Council, a group that advises the US Central Intelligence Agency. The report, which was made public in late September, 2002, and received a fair amount of media attention, has gone some way to reframing HIV/AIDS as a security concern.

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If we want a world that is defined by economic opportunity for all, and in which our security is guaranteed, and where terrorism has no place to hide, and where disputes are resolved by force of argument rather than force of arms—if we want that sort of world, Africa has to be part of it.

Former US President Bill Clinton during an October 9, 2002, address to the Woodrow Wilson International Center for Scholars in Washington, DC. Clinton's address followed his return from a five-nation African tour during which he called for debt relief for the world's poorest countries. He argued that debt relief should be linked directly to the HIV/AIDS pandemic, so that any country with an infection rate

higher than 15 percent of the population would qualify for relief on its debts if it spent the money on public health. Clinton also called on the Bush Administration to increase the US contribution to the Global Fund to Fight AIDS, Tuberculosis and Malaria from the current US\$300 million to US\$1.3 billion.

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A series of troubling reports have come out casting doubt on the [Bush] administration's commitment to the tradition of scientific excellence and science-based decision-making at HHS, suggesting that the tradition is being substantially undermined.

Excerpt from a letter to US Secretary of Health and Human Services (HHS) Secretary Tommy G. Thompson, as quoted in an October 22, 2002, Washington Post article entitled, "Ideology Rules at HHS, Democrats Say." A dozen US House of Representatives Democrats charged Thompson with using committee appointments, financial audits, and Internet sites to promote a conservative political agenda that sometimes runs counter to well-established science. With regard to HIV, the lawmakers questioned why the US National Institutes of Health (NIH) and US Centers for Disease Control and Prevention (CDC) have removed condom-related fact sheets from their Web sites. HHS Deputy Secretary Claude Allen labeled the complaints "rehash."

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The ultimate objective is to ensure that South Africans living with AIDS can have access to the treatment they need under conditions that will benefit them.

A sentence from an October 9, 2002, statement by the South African government

saying that it will seek to make antiretroviral drugs available through its public health-care system. This represents a major policy shift. In 2000, President Thabo Mbeki incited the ire of the global community by questioning, without any scientific support, the link between HIV and AIDS. Until April 2002, Mbeki and his government maintained that antiretroviral medications were poisonous.



What is most needed [by HIV-positive individuals in China] is treatment.

David Ho, Director of the New York-based Aaron Diamond AIDS Research Center, at an October 21, 2002, press conference in Beijing during which Chinese and US researchers launched a three-year HIV treatment study. The objective of the pilot study, which will take place in China's AIDS-stricken Yunnan Province, is to develop a strategy for nationwide antiretroviral treatment. The collaboration involves researchers from the Chinese Academy of Medical Sciences, the Aaron Diamond AIDS Research Center, and the Yunnan Provincial Center for Disease Prevention and Control.