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# IAPAC

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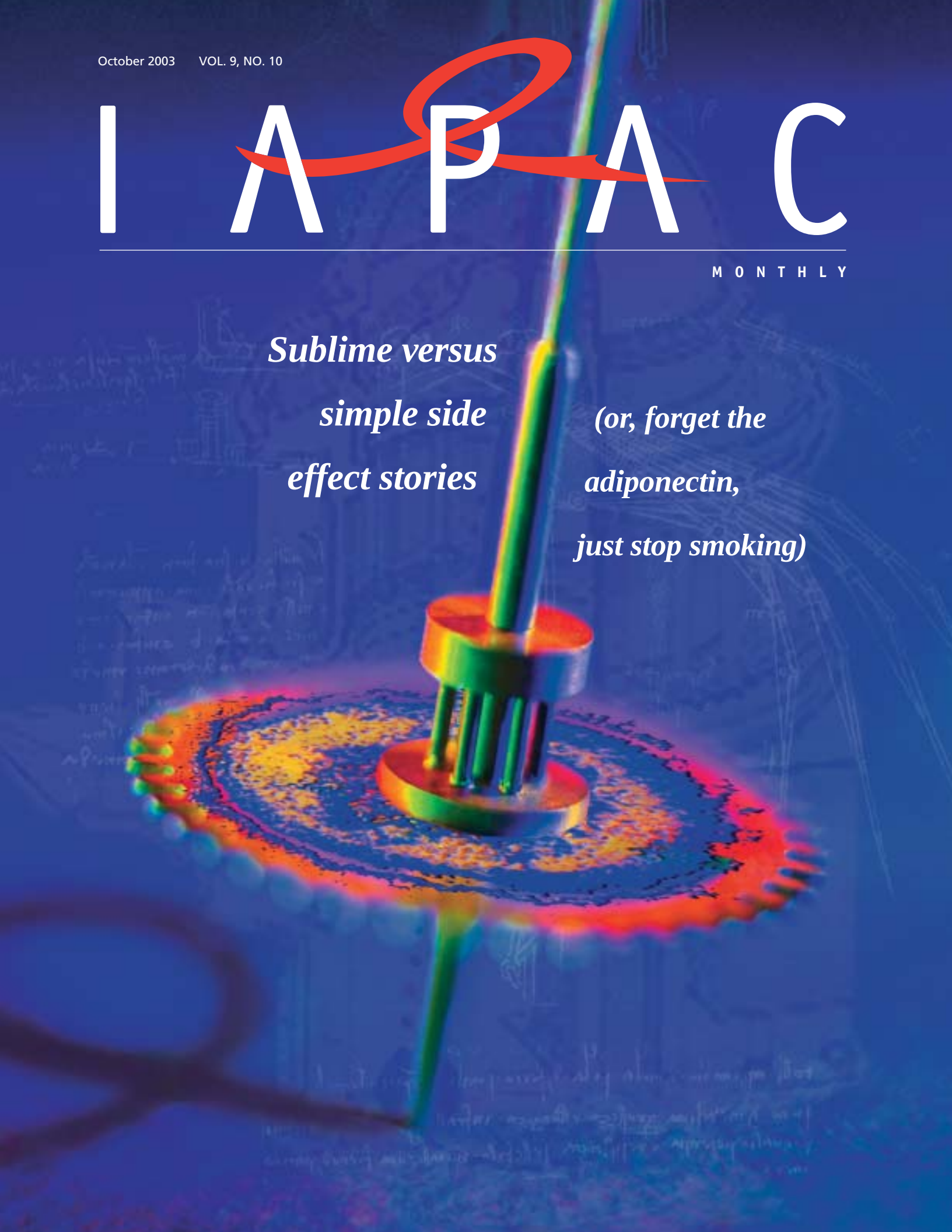
## *Sublime versus simple side effect stories (or, forget the adiponectin, just stop smoking)*



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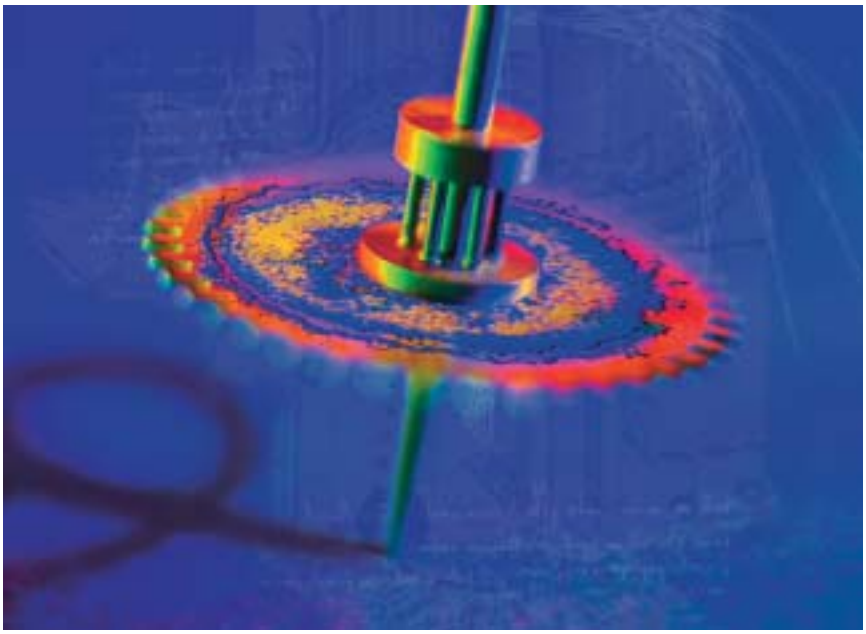

## Sublime versus simple side effect stories (or, forget the adiponectin, just stop smoking)

*Mark Mascolini*

The study of antiretroviral (and retroviral) side effects can be serpentine and knotty. But clinical research in this field often yields results as straightforward as the arc of Foucault's pendulum—as they did at the 5th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, held in Paris.

## DEPARTMENTS





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REPORT FROM THE PRESIDENT

# Putting off for tomorrow…

*José M. Zuniga*

Several times over the last year I have used this page to commend the US government for committing to a greater role in the global struggle against HIV/AIDS. The International Association of Physicians in AIDS Care (IAPAC) has always advocated that the world's wealthiest nations to fulfill their obligation to less affluent world neighbors. So when the United States, under the leadership of President George W. Bush and influential members of the US Congress, began to lay out a plan that would bring the world's most powerful nation into the fray in a manner more appropriate to its means, I felt it would be wrong to withhold recognition. As I said at the time, one must give credit where it is due and encourage future increases in commitment by recognizing those of the present.

Bush's decision to use the occasion of his January 28, 2003, State of the Union address to unveil a five-year, US$15 billion plan for treating and preventing HIV/AIDS in select African and Caribbean countries, was clearly historic because, as others also noted, dollar amounts were finally being discussed that were of a magnitude that fitted the disaster that is global AIDS—billions rather than millions. I was impressed again to see the bill authorizing spending on the global relief plan move through the US Senate and the US House of Representatives, in a display of comprise and political will, to receive the president's signature May 26, 2003, during a ceremony at which I was in attendance.

If one is wise to give due credit, however, one is also obligated to speak out when mistakes are made and opportunities are missed. Therefore, though I still believe that the leadership of the US government has come to take the AIDS pandemic as a serious threat and is committed to addressing it as such, recent developments speak to an unfortunate failure to do so in the best manner possible.

After a hard fought struggle to ensure that Congress authorized a fiscal year 2004 commitment of US$3 billion for the US Emergency Plan for AIDS Relief, the Bush Administration and Congress' leadership—Republican-controlled—have recently recanted on 100 percent commitment to the authorization amount of US$3 billion, setting the foreign HIV/AIDS expenditure for 2004 at around US$2 billion. This decision has been based on dubious concerns over the mechanisms through which these funds would see their way from national coffers to the programs that would benefit the millions of men, women, and children worldwide who are currently counting on assistance.

Both the Bush Administration and Congressional Republicans have expressed their skepticism about the ability of the Global Fund to Fight AIDS, Tuberculosis, and Malaria to use monies efficiently—despite a positive review of the Global Fund by the US General Accounting Office. Those at the fore of the recent appropriations cuts insist that a new national bureaucracy must be created within the US Department of State to disburse US donations, and because they feel this bureaucracy will require time to prepare itself before operating at full budget, they requested actual funding at two-thirds of the US$3 billion that Congress approved in May 2003 and for which members of both political parties have been taking credit.

The president and members of Congress opposed to spending any more than US$2 billion insist that greater annual funding will be budgeted for later years so that the full US$15 billion will be delivered within the five-year timeframe outlined in the plan. I hope that the full allotment, or more, is indeed disbursed. But I regret this halting start. Opportunities will be missed, and lives sacrificed, through a gradual roll out scheme—one that no visible evidence suggests is necessary. The truth is that the Global Fund, for instance, has already identified worthy, cost-effective programs that have withstood the scrutiny of technical review committees composed of highly esteemed medical, public health, and health management experts. However, the Global Fund will not be able to fund these programs because it has not received sufficient donations. If the political commitment to appropriately addressing HIV exists within the halls of Congress and at the White House, then there are institutions that could begin to implement full US funding in the immediacy. There is no acceptable excuse for delaying action, and I suspect that the real reason lies in the prioritization of other programs (and tax cuts?) in a time of budgetary retrenchment.

Such prioritization seems to have hit domestic AIDS programs as well. More and more US citizens unable to pay for expensive antiretroviral treatment are finding that government assistance is simply not there. Cuts or flat funding in both the House of Representatives' and Senate's appropriations for Ryan White CARE Act programs, with the exception of a negligible percentage increase for the AIDS Drug Assistance Program (ADAP), means that an increasing, and increasingly poor, number of HIV-positive patients in the United States will have reduced access to care and treatment. Indeed, the Senate voted down an amendment on September 11, 2003, that would have increased domestic AIDS spending to a level that can accommodate the growing need.

The result of this uncompassionate action—on a date on which the United States memorializes the death of thousands of innocents—will be needless suffering and death, turning back the clock on many hard-earned public health victories in the United States. As regrettable, this action seemingly breaks a promise that Bush made the day after his State of the Union address to not neglect domestic programs as government turns its gaze more fully to the international landscape.

In light of these losses at both the national and global levels, the temptation to lose hope that anything has been gained in the last year rears its head. We must not give into this temptation, however. We must be prudent and strategic in our approach, using what gains we have made to take our next steps forward.

While recent setbacks in the United States confirm the need for us to redouble our advocacy efforts, we must also take cognizance of the fact that despite a shortfall in global spending on the part of the US government (and others), it and many of these other Western governments are finally recognizing (and explicitly stating) that HIV/AIDS is a threat to global security that cannot be ignored. Both the moral import and the socio-economic evidence of the pandemic's impact on every world citizen has taken root in the deliberations of policy makers who hold the financial power to stem the destruction wrought by this plague. Rather than become deflated by our failure to fully achieve the funding that is required, we must instead galvanize around the power of these arguments, ones that these governments are coming to accept but still are not expanding into adequate commitments.

What is needed now is no longer the more difficult task of arguing for attention to the disease, but working with world leaders, and being critical when necessary, to craft an appropriate and thorough response. This is a task for which IAPAC and its members are well suited, and to which we remain committed. It is time for healthcare professionals with experience treating and preventing HIV disease to lend their help in shaping the struggle ahead. ■

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

# IAPAC appoints Vice President/ Chief Medical Officer

## African physician to oversee IAPAC's medical initiatives

The International Association of Physicians in AIDS Care (IAPAC) has named Mulamba Diese to the position of Vice President/ Chief Medical Officer. Diese, a physician highly experienced in the field of HIV medicine who was born in the Democratic Republic of Congo and is now a South African citizen, has served as Executive Director of IAPAC's African Regional Office (IAPAC-AFRO) since May 2002.

According to José M. Zuniga, IAPAC's President/CEO, it was largely Diese's success in leading IAPAC-AFRO that recommended him to the position of Vice President/Chief Medical Officer.

"Especially at a time when scale-up of antiretroviral therapy in resource-constrained countries is of increasing priority, IAPAC requires the expertise and wisdom that an African physician brings to the table," Zuniga explained. "He has done excellent work thus far in leading our Johannesburg office, and I am confident that he will excel in a position of expanded leadership."

Allen I. Freehling, Chair of IAPAC's Board of Trustees, echoed Zuniga's praise for Diese, citing his leadership as key to IAPAC's ongoing success on the African continent.

"Our President/CEO [José M. Zuniga] has chosen wisely in promoting an African physician to this position of expanded leadership. I am certain that IAPAC's Senior Management, with the addition of Mulamba Diese, is well positioned to forge ahead in these challenging times," said Freehling.

During Diese's tenure as Executive Director of the IAPAC-AFRO, his staff and a network of IAPAC members from various African countries trained more than 13,000 physicians and allied health professionals in the management of opportunistic infections, supported through funding from Pfizer Inc.'s Diflucan Partnership Program. Additionally, IAPAC-AFRO has offered technical assistance to various African governments; conducted training in antiretroviral therapy within IAPAC's Global AIDS Learning and Evaluation Network (GALEN); and coordinated interventions around the de-stigmatization of HIV infection and prevention of mother-to-child HIV transmission.

Mulamba Diese

"I am excited about the opportunity to leverage my experience in Africa to strengthen an IAPAC-wide push to make possible the World Health Organization (WHO) goal of three million people on antiretroviral therapy by 2005," Diese said. "By harnessing the strength of our membership, we will succeed in our efforts."

A search has begun in earnest for a new IAPAC-AFRO Executive Director. On an interim basis, Diese (who will be dually stationed in Geneva and Johannesburg) will oversee IAPAC's African operations. ■

# Sublime versus simple side effect stories

## (or, forget the adiponectin, just stop smoking)

*Mark Mascolini*

Paris is not for everyone. People who hate beautiful paintings, beautiful people, beautiful bridges, beautiful clothes, beautiful radio towers, beautiful vistas, and tip-top food, for example, had better stay away from Paris. But for the aesthete, the effete, and the wide-eyed, Paris is one swell town.

Even amidst this glut of pulchritude, though, the casual tourist with a scientific leaning doesn't have to look far for the most sublime *beau ideal* in the Ile de France. It's strung from the dome of the church of Saint Geneviève, also known as the Panthéon, just behind the Sorbonne, in the fifth arrondissement. It sways above the crypts of Voltaire, Rousseau, Hugo, and Zola. It's Jean-Bernard-Léon Foucault's pendulum. And it's sublime because it's so beautifully simple. Foucault started off like a lot of people who attended the 5th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV: practicing medicine. But ennui over things internal propelled him into the physical sciences, where he thrived, inventing the gyroscope, measuring the speed of light, discovering eddy currents, and proving that the Earth rotates on its axis. This last feat is where the pendulum comes in.

• *What is a Foucault pendulum?*
A Foucault pendulum is a heavy object (he used a cannonball) strung on a long wire and allowed to swing freely back and forth in a straight line.[1]

• *How does this prove the Earth rotates?*
If one sets the pendulum swinging and hooks up a magnet gizmo that lets it keep swinging without affecting the direction of the swing, over the course of a day the pendulum's path appears to change direction. (Foucault showed this by sticking a stylus on the end of his cannonball and scattering sand on the Panthéon floor.) By and by, the straight line of the pendulum's swing begins veering off on a clockwise course. But the pendulum is still swinging in the same plane. It's the floor beneath the pendulum—fixed to the Earth below—that's turning. When Foucault showed off his Panthéon pendulum, everyone saw he'd proved that the Earth rotates, and he did it for the first time without relying on astronomical observations. When Foucault built a pendulum in the Vatican, even the Pope became a believer.

• *What does this have to do with 5th Lipodystrophy Workshop?*
By the time Foucault enlightened His Holiness, all educated people believed the sun "rose" and "set" because the Earth turned on its axis. But no one had proved it with a simple apparatus. Foucault's *coup de théâtre* knocked the socks off his contemporaries because, once accomplished, it seemed so obvious.

• *Wait! Are you about to say someone at the 5th Lipodystrophy Workshop offered a stunningly simple explanation of HIV lipodystrophy and all of its entwined metabolic mix-ups?*
No. Quite the contrary. The 5th Lipodystrophy Workshop offered a welter of new studies pointing toward possible mechanisms of specific problems. One researcher even tied together a string of findings to suggest a link between lipoatrophy and insulin resistance. But no one dared advance a unifying hypothesis because, everyone agrees, many of the metabolic and morphologic changes now under study must have discrete causes.

No, this remains the era of thesis and antithesis, conjecture and contradiction, axiom and nullity, dead reckoning and the crabwise canter. An illustration:

**Do you believe in SREBP-1c genes?** Or do you have to be reminded that SREBP-1c—sterol-regulatory element-binding protein 1c—flips on genes that orchestrate lipid metabolism and distribution? The gene that gets SREBP-1c clicking, *SREBF1*, turns out to have a common variant labeled *SREBF1 3'332C>G* that Swiss researchers tied to high lipids in people taking antiretrovirals.[2] David Katz and Abbott colleagues looked at changes in lipids and *SREBF1* in 355 people taking lopinavir/ritonavir (LPV/RTV) or nelfinavir (NFV) in a randomized, double-blind trial [abstract 67]. The Abbott team found no "statistically significant or clinically meaningful relationship" between *SREBF1* genotype and total cholesterol or triglycerides. *SREBF1 3'332C>G* genotype did not predict hyperlipidemia in these treatment-naive people starting their first protease inhibitor (PI). Katz tried three different statistical analyses to confirm a gene link, and he came up empty-handed every time.

The Abbott team aptly observed that their findings "do not provide definitive evidence, positive or negative" about the impact of *SREBF1* genotypes on high lipids in people taking PIs. They studied a large, ethnically diverse population taking one of only two PIs, and they did not exclude people with a high body mass index or high pretreatment lipids. The Swiss did make those exclusions in an all-Caucasian population of 67 people tested for cholesterol and 44 tested for triglycerides. So researchers will have to keep studying *SREBF1* and other possible predictors of high lipids, genetic and nongenetic.

**Do lipoatrophy and insulin resistance have the same antiretroviral roots?** Here's another illustration of the mazelike mechanisms of metabolic problems, offered by one of the 5th Lipodystrophy Workshop's organizers, Jacqueline Capeau of Pierre and Marie Curie University in Paris. Surveying the past few years of side-effectology, she conjured a convincingly elaborate web of factors, cofactors, causes, and effects that starts with PIs and nucleoside reverse transcriptase inhibitors (NRTIs), wends its way via 16 arrows through three primary, three secondary, and one tertiary outcome, to two final endpoints—lipoatrophy and insulin resistance in liver and muscle (Figure 1).

Perhaps the most impressive aspect of Capeau's "hypothetical scheme" is that it pieces together enough primary research to suggest the cause of *two* problems that bedevil people taking antiretrovirals. Obviously, several of the variables boxed in Capeau's flow chart also figure in other "adverse events" scrutinized at this meeting. But it takes a supple enough mind just to array these 12 inputs and outputs without challenging the limits of credibility, audience attention span, and PowerPoint capacity.

## Keeping it simple

Why is this research so darn complicated? Because it involves a marvelous and messy living machine cobbled together through evolutionary chance and necessity, into which we now invite a relentless retrovirus and admix a slurry of cell-slamming drugs. Even in the nineteenth century, when medicine was much, much simpler, Foucault had the good sense to get out and start stringing cannonballs from church domes. As a result, he ended his career with more than one eureka moment. But the field of antiretroviral (and retroviral) side effects offered no such moments in Paris. Its doughty researchers must keep pecking away at prickly questions like why people taking indinavir (IDV) end up with plenty of plasma adiponectin. (More on that later.)

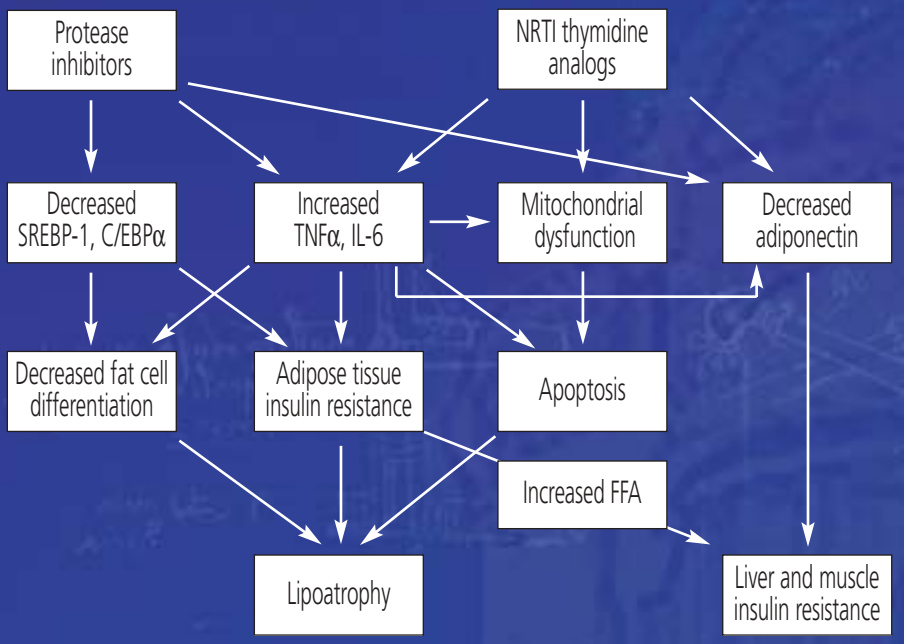
Yet the lambent light of simplicity did shine at the 5th Lipodystrophy Workshop, yielding easy-to-grasp conclusions and sometimes sturdy advice that can be applied today—because none of it depends on understanding arcane metabolic mechanisms. More than a half-dozen simple-sounding 5th Lipodystrophy Workshop studies belong to this genre, most of which this article will consider in its concluding section. But for those averse to delayed gratification, here are the half-dozen clinical nuggets:

- Manage PI-induced diarrhea with measures that work for other diarrhea.
- Get people with wide waists and insulin resistance to exercise.
- Nag people to stop smoking.
- Watch for preeclampsia in pregnant women taking triple therapy.
- Screen HIV-infected women for osteoporosis.
- Be aware of slow bone growth in HIV-infected children

## GLITAZONES AND STATINS

Down in the righthand corner of Jacqueline Capeau's "hypothetical scheme" of anti-

**Figure 1. Hypothetical mechanism for treatment-induced lipoatrophy and insulin resistance**




This model proposed by Jacqueline Capeau attempts to unify research on PI- and NRTI-induced changes that could promote lipoatrophy and insulin resistance. SREBP-1 (sterol-regulatory element-binding protein 1) and C/EBPα (CCAAT/enhancer-binding protein alpha) are fat cell differentiation markers. FFA is free fatty acid.

retroviral side effects (Figure 1) sits insulin resistance—the slow meltdown of insulin's regulatory effect on glucose. Back upstream, far above the bends and turns of apoptosis and mitochondrial dysfunction, lie the twin fonts of all these misfortunes, PIs and NRTIs.

Happily, the tongue-twisting thiazolidinediones, or glitazones, can reverse insulin resistance at a precise point in the dysregulatory cascade, by rousing PPAR-γ,[3] a critical receptor in tissues where insulin works hard—like liver, skeletal muscle, and fat. A key study by Capeau's group implicated downregulation of PPAR-γ in lipoatrophy.[4] On top of that, it turned out that glitazones can bulk up lean body mass, boost subcutaneous fat, and trim visceral fat in PI-treated people with diabetes.[5] So before even worrying over the hand wringing about mechanisms of toxicity (and there will be lots of that later), clinical researchers realized they had some potent pills already on the shelf.

The trailblazing thiazolidinedione, troglitazone, got yanked from the market when safer glitazones became available. One of its successors, rosiglitazone, turned up in the titles of three 5th Lipodystrophy Workshop reports.

## Will the pluses add up for rosiglitazone?

Before the 5th Lipodystrophy Workshop, two small studies put rosiglitazone to the test in people with HIV-related lipodystrophy, and they came up with contradictory results. A 30-person placebo-controlled trial in Finland, with 8 mg of rosiglitazone daily for 24 weeks, found no effect on subcutaneous or intra-abdominal fat.[6] Although fasting insulin and liver fat fell, triglycerides and cholesterol both climbed. In Italy a 6- to 12-week nonrandomized study of the same dose in eight people charted a 59 percent jump in insulin-mediated glucose disposal ($P$ = 0.02) and—unlike the Finnish study—a 21 percent drop in visceral adipose tissue ($P$ = 0.04) along with a 23 percent gain in subcutaneous adipose tissue ($P$ = 0.05).[7]

Colleen Hadigan (Massachusetts General Hospital, Boston) came to the 5th Lipodystrophy Workshop with the tie-breaker, a 27-person placebo-controlled trial of rosiglitazone at 4 mg daily for three months, followed by three months of open-label treatment for all study participants at 8 mg daily [abstract 12]. Everyone in the study had fat atrophy while taking a stable antiretroviral regimen. (About two thirds were taking a PI regimen and one third a nonnucleoside.) As in the Italian study, but not the Finnish trial, all study participants had insulin resistance (fasting insulin above 3 µU/mL or a two-hour insulin above 75 µU/mL after an oral glucose tolerance test). No one had diabetes. The 11 people randomized to placebo and the 16 randomized to rosiglitazone had a median CD4 count above 400 cells/mm$^3$, and three quarters had an undetectable viral load.

After three months, two measures of insulin sensitivity—glucose disposal and glucose/serum insulin—worsened in the placebo group and improved significantly in the rosiglitazone group ($P$ = 0.01 and $P < 0.05$ respectively). Body fat measured by bioelectric impedance analysis fell 5 percent in the placebo group and rose 15 percent in the rosiglitazone group, a significant between-group difference ($P = 0.04$). DEXA-measured leg fat rose about 4 percent with rosiglitazone while falling about the same amount with placebo, a difference that fell shy of statistical significance ($P = 0.06$). Subcutaneous fat area rose about 8 percent with rosiglitazone but less than 1 percent with placebo, a nonsignificant difference. These fat gains proved large enough for people taking rosiglitazone to notice during the blinded phase of the study. After six months of follow-up, subcutaneous fat had risen 12 percent in the rosiglitazone group.

Adiponectin, an insulin-sensitizing fat cytokine whose antiretroviral-induced decrease Capeau places on the causal pathway to insulin resistance (Figure 1), rose significantly more with rosiglitazone than with placebo (2.3 versus 0.1 µg/mL, $P < 0.01$). The adiponectin gain correlated positively and significantly with increased subcutaneous fat ($r$ = 0.59). Free fatty acid, whose increase may contribute to insulin resistance (Figure 1), swelled significantly in the placebo group.

But, as in the Finnish study, rosiglitazone had an unhappy effect on total cholesterol, which climbed among people taking the glitazone (+25 mg/dL) while falling in the placebo group (-16 mg/dL, $P < 0.01$).

Reviewing these three rosiglitazone studies at the 2nd IAS Conference on HIV Pathogenesis and Treatment, held a week after the 5th Lipodystrophy Workshop,[8] Morris Schambelan (University of California, San Francisco) underlined one salient feature that suggests why Hadigan and the Italian group[7] saw improvements in subcutaneous fat and the Finnish team[6] did not: The first two studies, but not the third, enrolled

people with insulin resistance. When insulin resistance is an entry requirement, Schambelan ventured, rosiglitazone seems to help boost subcutaneous fat.

A second three-month rosiglitazone study tends to support this suggestion, but with four volunteers it is too small to be decisive [abstract 74]. None of the four men recruited by Fehmida Visnegarwala (Baylor College of Medicine, Houston) had insulin resistance or a history of diabetes. All were taking PIs. After three months of rosiglitazone at the 8-mg daily dose, CT-measured mean abdominal subcutaneous fat rose nonsignificantly from 5,630 to 6,654 $mm^2$, while mean visceral adipose tissue fell nonsignificantly from 16,857 to 13,857 $mm^2$. Mean fasting glucose and insulin both fell significantly in this study (from 101 to 90 mg/dL, $P = 0.02$, and from 13.75 to 8.25 IU/mL, $P = 0.01$).

Yet again, rosiglitazone lifted lipids. Mean cholesterol climbed from 229.7 to 291.3 mg/dL and mean triglycerides from 352 to 643 mg/dL. Though neither of these gains proved statistically significant, the leap in total cholesterol took the group from the "borderline high" bracket to "high." The group started the study well above the safe triglyceride range of 10 to 190 mg/dL and got worse.

Neither Hadigan nor Visnegarwala found evidence of rosiglitazone-induced liver toxicity, the problem that torpedoed troglitazone. Guidelines proposed by Schambelan and others recommend avoiding glitazones with an aspartate or alanine aminotransferase more than 2.5 times the upper limit of normal.[9]

Together these studies support at least two conclusions about rosiglitazone.

- Rosiglitazone promotes insulin sensitivity in HIV-infected people with insulin resistance—a good thing, but not a surprise.
- Rosiglitazone, even at the lower dose Hadigan used, promotes hyperlipidemia in HIV-infected people—a sure drawback in people who may well have other reasons for high lipids.

Do these studies suggest rosiglitazone promotes good body fat changes in people with lipodystrophy—at least in those with insulin resistance? Of the two placebo-controlled trials, the Finnish study was powered to detect only big fat changes. Hadigan powered her study to spot significant changes in glucose and insulin, not body fat, she said. Hence, suggested David Cooper (University of New South Wales, Sydney), no one can say whether rosiglitazone eases lipodystrophy. An answer may come in ACTG 5082, which has randomized people with insulin resistance and excess abdominal fat to take metformin, rosiglitazone, or both.

The 5th Lipodystrophy Workshop yielded one more cautionary word on rosiglitazone: Just 4 mg daily lowers nevirapine (NVP) levels. A study by Mark Oette (Heinrich-Heine University, Düsseldorf) measured levels of NVP, efavirenz (EFV), lopinavir (LPV), NFV, and saquinavir (SQV) before and 28 days after people took rosiglitazone [abstract 115]. The insulin sensitizer had no substantial effect on EFV, LPV, or NFV, but the maximum concentration of NVP dropped 32 percent, the minimum concentration 36 percent, and the area under the curve 31 percent in four people taking the nonnucleoside with rosiglitazone ($P = 0.032$). Saquinavir levels also fell, but Oette could draw no conclusions because only one person was taking that PI.

### Statins, efavirenz, nelfinavir, CD4 cells

No one came to the 5th Lipodystrophy Workshop with news on statins, the prime choice for reining in runaway cholesterol. But the 2nd IAS Conference featured two studies with important news on these drugs.

Knowing that ritonavir (RTV) slices pravastatin levels, John Gerber (University of Colorado, Denver) gauged the effects of NFV on pravastatin in 14 healthy volunteers and the effects of EFV in 11.[10] The study started with three days of the statin, followed by two weeks of the statin plus the antiretroviral. Nelfinavir cut pravastatin exposure by a median of 47 percent (range -65 to +10 percent), and EFV lowered exposure by a median of 40 percent (range -73 to +28 percent). The findings could explain the lackluster response to pravastatin in ACTG A5087.[11]

If people are taking either of the antiretrovirals, or RTV, Gerber advised clinicians to "consider increasing the maximal dose of pravastatin two-fold." But he warned that physicians taking that course must monitor people closely for toxicity because his study showed that pravastatin concentrations don't drop in everyone taking NFV or EFV.

Clinicians starting a statin in someone responding well to antiretrovirals should know something else about these lipid lowerers: They may blunt CD4-cell spurts, according to results of a case-control study, but apparently only for six months or so.[12] Benigno Rodriguez (Case Western Reserve University, Cleveland) and coworkers worried that statins may derail CD4 gains because these antilipid drugs have a mélange of immunomodulatory effects. Their retrospective case-control study involved 73 people who started a statin during the first three years of potent antiretroviral therapy and had at least 12 months of follow-up after that. Rodriguez compared these cases with 146 antiretroviral-treated controls who never took a statin, matching cases and controls for age, gender (more than 90 percent were men), year of first potent regimen, and nadir CD4 count.

And the nadirs were low indeed, averaging 30 cells/$mm^3$ among cases and 33 cells/$mm^3$ among controls. By the time they started statin therapy, the cases had a significantly higher average count than controls, 440 versus 221 cells/$mm^3$ ($P < 0.0001$). But the two groups had equivalent proportions with undetectable viral loads. During the first six months of statin therapy, cases gained a median of 15 cells/$mm^3$ (interquartile range [IQR] -36 to 80 cells/$mm^3$) while controls gained a median of 45 cells/$mm^3$ (IQR 14 to 140 cells/$mm^3$, $P = 0.008$).

Rodriguez could not tie this effect to any baseline trait. The poster did not clarify whether the significantly higher CD4 count in the statin group when they started statins affected the relative gains in the two groups over the next half year. Perhaps not, because Rodriguez traced similar upward CD4 slopes in the two groups about one year after the statins started.

## WHY NRTIs DO WHAT THEY DO

The cause of lipoatrophy—and the toxic effects of NRTIs and PIs in general—have entered a decidedly unFoucaultian phase. Listening to some convincing studies at the 5th Lipodystrophy Workshop, one could come away advocating any of several toxicity theses, which do not necessarily mesh:

- Mitochondrial toxicity induced by the thymidine analogs zidovudine (AZT) and (especially) stavudine (d4T) leads to fat cell loss, dysfunction, or both, and thence to lipoatrophy.

- AZT and d4T upset fat cell viability and lower lipid content in those cells, while AZT induces insulin resistance in fat cells.
- The cytokines interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) drive altered differentiation and apoptosis of fat cells, and PIs or thymidine analogs may prod them on.

### Or is it all in the mind?

Another hypothesis, offered at the 2nd IAS Conference, holds that the cause of antiretroviral-related fat abnormalities is all in the mind—or, more precisely, the brain. Peter Reiss (Academic Medical Center, Amsterdam) outlined this work from Amsterdam's Institute for Brain Research.[13] Workers there suggest that certain antiretrovirals selectively influence sets of neurons and so upset the balance between sympathetic and parasympathetic output—and the results could be loss of subcutaneous fat and gains in visceral fat. Here's something new.

In a murine model the Institute team selectively denervated an intra-abdominal fat pad on one side of the animal, but not on the other. Parasympathetic denervation led to such marked drops in uptake of glucose and free fatty acid into fat cells that these adipocytes could no longer store fat. At the same time, the activity of lipase, responsible for breaking down fat, increased. Furthermore, these workers showed, within sympathetic and parasympathetic nuclei lie discrete neuron sets that project to (a) intra-abdominal fat, and (b) subcutaneous fat.

This research "offers the possibility," Reiss proposed, "that the central nervous system can selectively control adipose tissue in different parts of the body, and it can do so by balancing out output from the sympathetic and parasympathetic nervous system." So the fat abnormalities of lipodystrophy may—"and this is a question mark," Reiss stressed—represent what he coined "selective autonomic neuropathy."

Where do the antiretrovirals come in? Perhaps not coincidentally, certain NRTIs, like d4T and didanosine (ddI), have earned a reputation for neurotoxicity *and*, in d4T's case, lipodystrophy. So, the idea goes, these drugs may rile critical neurons and upset the balance between sympathetic and parasympathetic output and thus promote subcutaneous fat loss and visceral fat gain. The kicker here is that the brain region involved is not protected by a blood-brain barrier and so would seem defenseless against neurotoxic drugs.

If this fascinating thesis proves true (and Reiss noted that the data buttressing this scheme should be published soon), it will only increase questions about the mitochondrial and cytokine theories. David Nolan, Jacqueline Capeau, and others proffered the latest evidence supporting those postulates at the 5th Lipodystrophy Workshop:

### Depleting mighty mitochondrial DNA

The mitochondrial hypothesis of NRTI toxicity has gained currency partly because much of the research involves human beings taking drugs like d4T and AZT, then losing subcutaneous fat as various cells shed mitochondrial DNA (mtDNA). David Nolan, who has spearheaded this work in Simon Mallal's group at the Royal Perth Hospital, spelled out his latest findings in people taking d4T or AZT and in control groups of antiretroviral-naive HIV-infected people [abstract 18].

Measuring mtDNA in biopsied subcutaneous fat, Nolan counted 1,288 copies/cell in 24 treatment-naive controls, 726 copies/cell in 29 people taking AZT (a 44 percent drop, $P = 0.006$), and 240 copies/cell in 28 taking d4T (an 81 percent plummet, $P < 0.001$ versus controls and people taking AZT). Another 11 people taking NRTIs other than AZT or d4T had mtDNA numbers equivalent to those of untreated controls.

PI use and CD4 counts at the time of biopsy did not affect mtDNA levels in subcutaneous fat. But mtDNA quotients did correlate with adipocyte toxicity gauged by confocal microscopy. As mtDNA levels dropped, Nolan saw adipocyte pleomorphism that progressed to "adipocyte loss with marked macrophage infiltration and disordered tissue architecture."

Clinically, these changes tracked with levels of subcutaneous fat in the leg, which measured 24 percent in the treatment-naive controls, 17 percent in the people taking AZT, and 11 percent in the people taking d4T.

And when people swap d4T for another nucleoside, adipocytes regain mtDNA copies. That conclusion came from a 16-person substudy of an open-label trial in which 118 people traded d4T for abacavir (ABC) or AZT/lamivudine (3TC) [abstract 90]. Grace McComsey (Case Western Reserve University, Cleveland) counted an average 194 mtDNA copies/cell before the switch and 430 copies/cell 48 weeks after the switch ($P = 0.01$). As she reported earlier, the nucleoside tradeoff yielded gains in arm, leg, and subcutaneous adipose fat, and a drop in visceral adipose fat. People switching to ABC had better fat changes than those switching to AZT/3TC.

What happens to mtDNA in other cells when people start taking NRTIs? Ulrich Walker (University of Freiburg) learned that mtDNA also disappears from liver cells of people taking d4T, ddI, or zalcitabine (ddC), a loss that could contribute to high lactates in people taking the d-drugs [abstract 17]. He used Southern blotting to measure mtDNA in liver cells from people biopsied because of diffuse liver pathology, high liver enzymes, or active hepatitis C virus (HCV) infection.

Compared with HIV/HCV-coinfected people not taking antiretrovirals, those taking a d-drug had 40 percent less mtDNA in liver cells ($P < 0.001$). HIV/HCV-coinfected people taking AZT, 3TC, or ABC, but not a d-drug, had mtDNA levels equivalent to those of the untreated group. Among d-drug takers, those using only d4T had greater mtDNA depletion than those taking ddI or ddC. Lactate levels proved significantly higher in the d-drug group ($P = 0.017$) and in the non-d-drug group ($P = 0.042$) than in the untreated people with HIV/HCV coinfection.

Yet work at the University of Barcelona Hospital Clinic by Sònia López showed that it doesn't take d-drugs or other nukes to deplete mtDNA—it just takes HIV, at least in peripheral blood mononuclear cells (PBMCs) [abstract 54]. López compared PCR-measured mtDNA in PBMCs from 22 antiretroviral-naive people with HIV infection and 27 age- and gender-matched seronegative controls. The HIV group had 68 percent of the mtDNA per cell measured in the control group ($P < 0.01$). This work reflected results already published by a team at the University of British Columbia,[14] who found that antiretroviral-treated people with symptomatic hyperlactatemia had a 68 percent lower mitochondrial-to-nuclear DNA ratio in blood cells than did uninfected controls.

### How AZT, d4T, and PIs disrupt fat cells

David Nolan's work documented mtDNA depletion in fat cells with both thymidine nucleoside analogs, but a significantly greater loss with d4T than with AZT (see preceding section). Using different yardsticks, Martine Caron in Jacqueline

**Table 1. Effects* of NRTIs on cultured adipocytes**

| | *Increased cytotoxicity* | *Increased apoptosis* | *Decreased lipid accumulation* | *Insulin signal transduction* | *Decreased lipogenesis* |
|---|---|---|---|---|---|
| AZT | Yes | Yes | Yes | Yes | Yes |
| d4T | Yes | Yes | Yes | No | Yes |
| ddI | No | No | No | No | No |
| 3TC | No | No | No | No | — |
| ABC | No | No | No | No | — |
| AZT/3TC | Yes | No | Yes | Yes† | — |
| AZT/3TC/ABC | Yes | No | Yes | Yes† | — |

*Cytotoxicity was assessed by MTT hydrolysis, apoptosis by FACS, lipid accumulation by oil red O staining, insulin signal transduction by phosphorylation of the insulin receptor beta subunit and by activation of ERK 1/2 and Akt/PKB, and lipogenesis by $C_{14}$ glucose incorporation in lipids.

†ABC and 3TC increased the effect of AZT alone.

Source: Martine Caron, abstract 10.

Capeau's group at Pierre and Marie Curie University also showed that the thymidine analogs stand out as adipocyte disrupters [abstract 10]. She used cultured adipocytes to gauge the effects of AZT, ddI, d4T, 3TC, and ABC on cell differentiation, lipid accumulation, and response to insulin.

Caron noted that the dose of each drug equaled the maximum concentration given for at least 11 days, levels that would never be sustained in people taking these nucleosides (1 µM AZT, 10 µM d4T, 10 µM ddI, 10 µM 3TC, and 4 µM ABC). Under these experimental conditions, she found that AZT and d4T upset fat cell viability and slowed lipid accumulation in those cells, but ddI, 3TC, and ABC did not (Table 1). Zidovudine but not the other NRTIs induced insulin resistance in fat cells. Adding 3TC or 3TC/ABC to AZT made the insulin resistance worse.

Jacqueline Capeau collared two other potential lipoatrophy culprits, the cytokines TNF-α and IL-6 [abstract 9]. Her study of 26 people taking PIs and NRTIs and 18 uninfected controls linked higher expression of these cytokines to altered differentiation and increased apoptosis of subcutaneous abdominal fat cells.

Most HIV-infected study participants were taking IDV ($n$ = 15) or NFV ($n$ = 9), usually with d4T and 3TC. Capeau matched them to uninfected controls by age and body mass index. Compared with controls, the HIV group had significantly more fibrosis in fat cells and macrophages per field ($P$ = 0.02 for both). The apoptosis rate in fat cells measured 18.4 percent in antiretroviral-treated people versus 5.6 percent in controls ($P$ = 0.005). Capeau found a negative correlation between apoptosis and the cell differentiation markers C/EBP-α ($r$ = -0.73, $P$ = 0.005) and SREBP-1 ($r$ = -0.66, $P$ = 0.01).

Levels of IL-6 mRNA were three times higher in the HIV group than in controls, mirroring the higher level of TNF-α Capeau had found earlier. Expression of those cytokines correlated inversely with the differentiation markers C/EBP-α and SREBP-1 and positively with apoptosis ($r$ = 0.694, $P$ = 0.01 for IL-6 and $r$ = 0.504, $P$ = 0.05 for TNF-α).

"Since these two cytokines act at the level of adipose tissue through autocrine/paracrine mechanisms," Capeau concluded, "these results argue for a deleterious role of adipose tissue cytokines not only in altered [fat cell] differentiation but also in increased apoptosis, which could be responsible for clinical lipoatrophy."

Studying 3T3-F442A adipocytes, Simon Jones (University of Liverpool) found that PIs drive IL-6 expression while both PIs and NRTIs stimulate TNF-α [abstract 11]. Jones compared mRNA levels of the cytokines in adipocytes exposed to 20 µM of AZT, d4T, IDV, RTV, and SQV with levels in unexposed adipocytes. Saquinavir boosted IL-6 mRNA expression 28.54-fold and RTV boosted expression 17.85-fold ($P$ < 0.001 for both). The other drugs had little effect on IL-6. All drugs studied magnified expression of TNF-α.

As Capeau concluded in a review talk at the 2nd IAS Conference,[15] studies like these show that AZT and d4T toxicities do not depend solely on depletion of mtDNA.


Research seeking to explain lipoatrophy, though proceeding full bore, remains in a formative stage. But that hasn't stopped clinicians and people with HIV from deciding which nucleosides they do and do not want to use. In its 2003 draft antiretroviral guidelines, the British HIV Association reflected the growing sentiment against d4T as a first-line NRTI, advising that "combinations including d4T are not recommended because of increasing evidence of its role in the development of lipodystrophy and abnormal lipid profiles."[16] But the July 14, 2003, update of US Department of Health and Human Services (DHHS) guidelines sticks with d4T as a first-line choice.[17]

Clinical concern over d4T-induced toxicity derives not only from cell studies like those reviewed above, but also from several drug-switch trials and cohort studies implicating d4T in lipoatrophy. More research of this ilk appeared at the 5th Lipodystrophy Workshop. But two studies—one at the 5th Lipodystrophy Workshop and one at the 2nd IAS Conference—saw d4T in a new (and more flattering) light. And work by d4T's maker, Bristol-Myers Squibb, in collaboration with the University of Colorado, echoed an earlier study in finding a higher risk of lipoatrophy in people who start treatment at lower CD4 counts.

### Starting with and switching from d4T

The latest US DHHS guidelines abandon the earlier menu of antiretrovirals in each drug class from which one could concoct a starting regimen.[17] Instead, the DHHS experts pick specific combinations as "preferred" first-line options. The pillar of initial therapy, they advise, should be LPV/RTV or EFV. The nucleoside buttresses are:

- With EFV: 3TC + (AZT or tenofovir [TDF] or d4T)
- With LPV: 3TC + (AZT or d4T)

Emtricitabine (FTC) had not been licensed when the DHHS panel devised this list. Given its superiority to d4T in a randomized, placebo-controlled trial of first-line regimens,[18] it will most likely make the "A-team" on the next update. A more notable exception from the DHHS list is the once-familiar pairing of d4T and ddI. That duo lost to AZT/3TC in ACTG 384.[19] At the 5th Lipodystrophy Workshop, results of a CPCRA 058 ("FIRST") substudy found a higher rate of fat abnormalities among

**Table 2. Body weight and shape measures after 32 months with two NRTI duos**

| | Units/month (standard error) | | |
|---|---|---|---|
| | *ddI/d4T (n = 46)* | *3TC/ABC (n = 50)* | *P* |
| Body mass index (kg/m$^2$) | -0.03 (0.01) | 0.04 (0.01) | <0.01 |
| Body cell mass (kg) | 0.02 (0.01) | 0.04 (0.01) | <0.01 |
| Total body fat (kg) | -0.09 (0.02) | 0.10 (0.02) | <0.01 |
| Arm circumference (cm) | -0.04 (0.01) | 0.01 (0.01) | <0.01 |
| Waist circumference (cm) | -0.04 (0.03) | 0.01 (0.01) | <0.01 |
| Hip circumference (cm) | -0.19 (0.04) | 0.09 (0.04) | <0.01 |
| Thigh circumference (cm) | -0.08 (0.02) | 0.01 (0.01) | <0.01 |
| Triceps skinfold (mm) | -0.13 (0.02) | 0.01 (0.02) | <0.01 |
| Subscapular skinfold (mm) | -0.03 (0.02) | 0.05 (0.02) | <0.05 |
| Abdominal skinfold (mm) | -0.15 (0.04) | 0.12 (0.03) | <0.01 |
| Thigh skinfold (mm) | -0.12 (0.03) | -0.01 (0.03) | <0.01 |

Study participants were antiretroviral naive when beginning one of the NRTI pairs with a PI, an NNRTI, or both.
Source: Subhasree Raghavan, abstract 13.

naive people starting a ddI/d4T regimen than in those starting with 3TC/ABC [abstract 14].

CPCRA researchers randomized 1,400 people to begin therapy with a PI, a non-nucleoside, or both, along with either ddI/d4T or AZT/3TC. Subhasree Raghaven (Harlem Hospital, New York) reported body composition results of the NRTI substudy, which involved 46 people taking ddI/d4T and 50 taking 3TC/ABC. The substudy group was 64 percent African American, 13 percent Latino, and 28 percent female. The two NRTI groups started therapy with similar median CD4 counts (268 cells/mm$^3$ for ddI/d4T and 234 cells/mm$^3$ for 3TC/ABC) and viral loads (4.85 and 5.03 log copies/mL, respectively). Seventy percent in each NRTI group also took a PI.

After a median 32.6 months of follow-up, the ddI/d4T group did worse than the 3TC/ABC group in every morphologic measure recorded (Table 2). Insulin levels climbed more in the ddI/d4T group than in the 3TC/ABC group (5.2 versus 0.3 µM/mL). CPCRA statisticians had not yet correlated these changes with CD4 count, viral load, race, gender, or other variables.

A possible limitation of this study is its heavy reliance on anthropometric measurements—skinfolds and body circumference—rather than on DEXA or CT scans. Even when personnel are centrally trained, as in this trial, results can vary from one technician to the next. In the already-mentioned study of 118 people who traded d4T for ABC or AZT/3TC, Grace McComsey found no correlation between 48-week DEXA-measured gains in arm or leg fat and physical measurements of arms and legs [abstract 90]. Still, the lock-step consistency of the CPCRA data on every variable assessed is hard to ignore.

The MITOX study was the first nucleoside switch trial to chart improvements in peripheral fat among people who traded d4T or AZT for ABC.[20] A two-year update of that study by Andrew Carr (St. Vincent's Hospital, Sydney) showed a continuing slow accrual of limb fat in switchers [abstract 16]. Two years after the randomized switch, people who had lost about half of their limb fat had gained back about one third of that loss. It took about six years of NRTI therapy for these 106 study participants to lose half of their limb fat, Carr observed, and at this pace it could take that long to get it back.

MITOX randomized people—nearly all of them white men and 85 percent of them taking d4T—to continue d4T or AZT or to switch to ABC. At that point the ABC switch group averaged 3.54 kg of limb fat and the nonswitch group averaged 3.75 kg—about half of the 7 or 8 kg that most men have. After 24 weeks the ABC group had gained 0.39 kg of limb fat, significantly more than the 0.09 kg in the d4T-or-AZT group ($P = 0.016$). But gains were so modest that neither the men nor their clinicians noticed them. After 24 weeks everyone could switch to ABC.

In an intent-to-treat analysis at 108 weeks, people originally randomized to ABC had gained 1.26 kg in limb fat (+36 percent), compared with 0.49 kg (+13 percent) among those originally randomized to stay with d4T or AZT, a significant difference ($P = 0.008$). In a 108-week on-treatment analysis, people who originally switched to ABC gained 1.29 kg (+36 percent), those who switched to ABC by week 24 gained 0.55 kg (+15 percent), and those who stayed with d4T or AZT gained 0.16 kg (+4 percent). A multivariate model found three independent predictors of greater limb fat gains:

- Lower baseline bone mineral density (coefficient 0.53, $P = 0.006$)
- Shorter duration of AZT before randomization (coefficient 0.017, $P = 0.024$)
- Shorter duration of d4T during the study (coefficient 0.065, $P = 0.004$)

Carr added that the limb fat gains—which plumped up legs more than arms—varied considerably from person to person. Visceral adipose tissue, CD4 counts, viral loads, and glycemic variables did not change significantly through 108 weeks of follow-up.

Although MITOX now offers the longest and strongest evidence that stopping a thymidine analog—usually d4T—can restore peripheral fat, some observers want more proof. In his 2nd IAS Conference review of 5th Lipodystrophy Workshop studies,[8] Morris Schambelan cautioned that "whether [fat gains] will continue on an upward trend remains to be determined."

Tracking DEXA-measured leg fat changes in 72 white men starting a regimen containing d4T or AZT, David Nolan saw a significantly greater loss in those taking d4T than in those taking AZT through 36 months of treatment ($P = 0.02$) [abstract 95]. He estimated a 45 percent fat loss in the d4T group versus 30 percent in the AZT group. PIs, used by more than 70 percent in each group, did not affect the results; nor did baseline CD4 count or concomitant treatment with ddI.

Men who traded d4T for AZT saw no further drop in leg fat through an average 22 months (range 3 to 40 months). But they did not regain leg fat, as people did in McComsey's study of switching to ABC or AZT [abstract 90] or in Carr's study of switching to ABC [abstract 16]. In Nolan's analysis, controls matched to d4T-AZT switchers for duration of treatment and taking d4T the whole time continued losing fat ($P < 0.01$ compared with switchers).

## Safer ways to use d4T?

A Thai study of 54 men and 26 women with lipoatrophy while taking d4T registered

**Table 3. Lower rate of lipoatrophy with d4T at higher CD4 nadir**

| | *First-line d4T (n = 21)* | *d4T after AZT (n = 23)* |
|---|---|---|
| Nadir CD4 percent | 19 (3 to 31) | 16 (0 to 34) |
| Nadir CD4 count (cells/mm$^3$) | 358 (40 to 908) | 212 (0 to 523) |
| Highest viral load (RNA copies/mL) | 95,499 | 223,872 |
| Time on d4T (months) | 46 (25 to 76) | 27 (9 to 69) |
| New lipodystrophy, *n* (%) | 2 (10) | 10 (42) |
| New lipoatrophy, *n* (%) | 1 (5) | 6 (29) |
| Nadir CD4 percent and number in those with lipoatrophy | — | 13, 122 |
| Nadir CD4 percent and number in those without lipoatrophy | — | 18.4, 358 |
| New peripheral neuropathy, *n* (%) | 2 (10) | 4 (17) |

Source: Gary Blick, abstract 76.

fat gains after cuts in the d4T dose.[21] Although this strategy proved safe—no one had a viral breakthrough from below 50 copies/mL—gauging the precise impact of lower dosing is difficult because the investigators relied almost solely on clinical judgment to rate fat gains.

Everyone had a sub-50-copy viral load for at least six months when the study began, though CD4 counts ranged from a scary 35 cells/mm$^3$ to a hefty 922 cells/mm$^3$ (mean 334 cells/mm$^3$). Mattana Hanvanich (Chulalongkorn University, Bangkok) and colleagues at Bumrungrad Hospital classified lipoatrophy as mild in 22 people, moderate in 41, and severe in 17. They trimmed the d4T dose according to the following scheme:

- If weight ≥60 kg (mean 67.2, range 60 to 101 kg), lower dose from 40 to 30 mg twice daily.
- If weight <60 kg (mean 50.4, range 32 to 59 kg), lower dose from 30 to 20 mg twice daily.
- If improvement is unsatisfactory, lower dose to 50 percent or less of current recommended dose.

Improvement appeared to be faster in people with more moderate lipoatrophy. Fifty-six study participants (70 percent) needed the additional reduction to 50 percent less of the standard dose. Overall weight gains averaged 0.78 kg in the mild group, 2.2 kg in the moderate group, and 1.1 kg in the severe group. Abdominal girth (not further defined) dropped during the study. All viral loads stayed under 50 copies/mL through a median 93 weeks of follow-up (range two to 309 weeks). Eight people (10 percent) had traded d4T for ABC at the time of the analysis.

Because HIV Outpatient Study (HOPS) investigators linked nadir CD4 count—but no specific antiretroviral—to development of lipoatrophy,[22] clinicians in Connecticut and New York decided to see if d4T may be safer in people who started it with more T cells [abstract 76]. Their retrospective analysis compared 21 people who took d4T as part of their first regimen with 23 who took it after trying AZT.

Gary Blick (Circle Medical Group, Norwalk) reported a mean age of 46 years in both groups, and about 40 percent in each group were women. The first-line d4T group had a higher percentage of nonwhites (80 versus 42 percent) and a higher percentage of nongays (80 versus 58 percent). The nadir CD4 percent and nadir CD4 count were substantially higher in the first-line group, and the highest viral load substantially lower in that group (Table 3). Despite a longer duration of d4T therapy in the first-line group, those people had a much lower incidence of clinically judged lipodystrophy and lipoatrophy (Table 3).

Blick concluded that current DHHS guidelines, designed to avert or hold off side effects by delaying treatment until the CD4 count falls below 350 cells/mm$^3$, "may be placing patients at increased risk of . . . lipoatrophy and peripheral neuropathy." But, as results of other cohort studies suggest, that may be true only if people start therapy with d4T. Blick and colleagues promised a complete analysis of 85 people treated with d4T as a first or second thymidine analog. The results will be interesting if the authors offer statistical correlations between CD4 nadirs and the later emergence of lipoatrophy. The current analysis did not specify the nadirs of people in whom side effects developed, only the averages and ranges for each group.

Nadir CD4 count independently predicted lipoatrophy in a database analysis by Christopher Dezii (Bristol-Myers Squibb) and Kenneth Lichtenstein (University of Colorado, Denver) [abstract 78]. They calculated that, for every 100-cell increment in the nadir count, the risk of fat wasting dropped 18 percent. The correlation looked most convincing in CD4 brackets below 350 cells/mm$^3$ (Table 4), because more than 90 percent of people in those strata were taking antiretrovirals.

Dezii analyzed fat trends in 7,980 HIV-infected people in the Cerner Corporation's HIV Insight database. To ensure that he counted only new cases of fat build-up or loss, he included only people with no reported fat abnormalities for six months before such a report. As in any database analysis of this size, the lipodystrophy diagnosis depended on a clinician's subjective impression of "lipodystrophy without fat wasting" or "fat wasting" of the limbs, hips, buttocks, face, or neck.

The cohort had a mean age of 38.9 ± 8.45 years, a mean follow-up of 3.67 ± 2.99 years, and a mean HIV infection duration of 7.77 years. Most (85 percent) were men, 58 percent were Caucasian, and 29 percent were African American. Dezii charted a significant increase in the incidence of fat wasting—but not of lipodystrophy without wasting—in groups with lower CD4 nadirs (Table 4). Logistic regression modeling controlling for age, race, HIV duration, body mass index nadir, and CD4 nadir—but not antiretroviral exposure—found a higher risk of fat wasting with a lower CD4 nadir, a lower body mass index nadir, longer HIV duration, male gender, or white race. The CD4 result confirms Lichtenstein's similar finding in the HOPS cohort.[22]

### Medicine that mends mitochondrial damage?

Avoiding or retiring the more toxic antiretrovirals and starting certain antiretrovirals earlier may trim the risk of lipoatrophy, as the foregoing studies suggest. But many people don't get their HIV diagnosis until their T cells fall into double digits, and many others are already paying the toxic price of drug therapy. So wouldn't it be nice if you could just take a pill that would reverse the damage already done?

The University of Freiburg's Ulrich Walker thinks such a medicine may already be for sale in Europe, a dietary supplement called NucleomaxX with Mitocnol,[23] at least if the drug toxicities are of the mitochondrial kind. Cell studies in his lab suggest that Mitocnol's essential ingredient,

**Table 4. Lipoatrophy incidence correlates with lower CD4 nadirs**

| CD4 nadir (cells/mm³) | n (%) | Taking antiretrovirals (%) | Incidence of fat wasting (%)* | Incidence of lipodystrophy without wasting (%) |
|---|---|---|---|---|
| 0 to 99 | 2,547 (32) | 95 | 10.7 | 4.9 |
| 100 to 199 | 1,364 (17) | 94 | 8.3 | 5.2 |
| 200 to 349 | 1,876 (24) | 90 | 7.1 | 5.1 |
| 350 to 499 | 1,234 (16) | 81 | 6.5 | 4.6 |
| ≥500 | 959 (12) | 68 | 5.0 | 3.0 |

*$P < 0.0001$.
Source: Christopher Dezii, abstract 78.

uridine, can correct mitochondrial miscues [abstract 19].

After exposing liver cells (HepG2 hepatocytes) to 177 nM of ddC, Walker recorded severe mtDNA depletion (to 8 percent of normal levels), a steep drop in cell proliferation (to 20 percent of normal), severe intracellular steatosis (fat buildup), and up to a 350 percent jump in lactates. Uridine restored mtDNA levels to about 65 percent of normal and thereby "fully normalized" cell proliferation and intracellular lactate and lipid levels. Uridine worked this magic even when Walker continued treating the cells with ddC. The best results came at the highest uridine dose, 200 µM. Similar experiments with d4T and AZT—but not ddI—had similar results. Walker also found that uridine does not alter the 50 percent or 90 percent inhibitory concentrations of current nucleosides.

Given at a dose of three sachets per day for four days, NucleomaxX with Mitocnol reversed cellular toxicities in a person taking d4T. Walker and his colleagues have taken up to twice the recommended dose of this supplement, and no side effects emerged in this preliminary test. (The recommended dose is three sachets daily for three days, then no treatment for the rest of the month.) He plans formal tests to see whether this agent can help people with suspected mitochondrial toxicities such as lipoatrophy and polyneuropathy.

## EYES ON PIs AND NNRTIs

Much of the basic research laid out at the 5th Lipodystrophy Workshop involved NRTIs, but PIs did not escape scrutiny. Probably the most revealing study—because it plugs a big hole in the lipodystrophy databank—examined the effects of PI-based therapy in a large cohort of American women. Other work tied IDV to endothelial dysfunction and—in healthy volunteers—to higher hepatic glucose production. Stopping PIs for 96 weeks barely improved glycemic dysregulation in people with severe lipodystrophy. In the nonnucleoside arena, two teams disagreed on how fast toxicity forced people to stop EFV or NVP.

### How PIs perturb fat in women

The FRAM study identified lipoatrophy as the main feature of lipodystrophy in HIV-infected men.[24] Compared with uninfected men enrolled in a heart disease cohort, FRAM men with HIV had less peripheral *and* central fat. But as Kathleen Mulligan (University of California, San Francisco) observed at the 5th Lipodystrophy Workshop, the HIV-infected men in FRAM tended to be lean at baseline, while HIV-infected women in the United States tend to be overweight or obese. So what happens when these women start taking antiretrovirals?

To find out, Mulligan and colleagues in the Women's Interagency HIV Study (WIHS) ran a cross-sectional comparison of four groups [abstract 15]:

- 78 women without HIV infection (but at risk)
- 57 HIV-infected women not taking antiretrovirals
- 36 HIV-infected women taking a PI regimen
- 43 HIV-infected women taking a non-PI regimen

They excluded pregnant or lactating women, women on hormone replacement therapy or steroids, and women weighing more than 120 kg. Nearly half in the HIV and non-HIV groups were African American, and 40 percent in each group were Hispanic. More than half in each group were overweight or obese. The women with HIV were older (41 versus 36 years, $P < 0.001$), and more women with HIV had one or more pregnancies (85 versus 53 percent, $P < 0.0001$). Fewer HIV-infected women smoked cigarettes, though most in both groups smoked (63 percent with HIV versus 76 percent without HIV, $P = 0.04$).

Body mass index was significantly lower in the women taking a non-PI regimen (about 26 kg/m$^2$) than in the HIV-infected untreated group (about 28 kg/m$^2$, $P = 0.03$) or in the HIV-uninfected group (about 30 kg/m$^2$, $P = 0.01$). The women taking PIs averaged about 28 kg/m$^2$ but did not differ significantly from the other groups. Total fat was also significantly lower in the non-PI treated group than in the HIV-infected untreated women ($P = 0.006$) or the HIV-uninfected women ($P < 0.01$). The PI group was closest to the untreated group in total fat but again did not differ significantly from the other groups.

Compared with the HIV-uninfected women, leg fat was lower in both the PI group ($P = 0.01$) and the non-PI treated group ($P < 0.001$). But the women taking a PI didn't differ from the non-HIV group or the untreated group in trunk fat, whereas the non-PI treated women had significantly less trunk fat than the untreated ($P = 0.02$) or uninfected women ($P < 0.001$).

In a multivariate model controlling for age, race, smoking, exercise, number of live births, CD4 count, viral load, and d4T treatment, five factors proved significant predictors of lower leg fat—not being African American, having a CD4 count below 200 cells/mm$^3$, taking d4T, cigarette smoking, and exercising more than six hours a week. Except for race and d4T, the same factors correlated with less trunk fat.

Mulligan advanced the following conclusions:

- As in men with HIV infection, antiretroviral-treated women have less leg fat than untreated groups or HIV-uninfected controls, despite the high prevalence of obesity among these women.
- Women taking PIs, but not those taking a non-PI regimen, appear to conserve trunk fat.
- The multivariate analysis showed that increasing age does not correlate with decreasing peripheral fat, as age does in HIV-infected men.
- Besides genetic and disease-related factors, two lifestyle variables—smoking and exercise—correlated with lower fat levels.

Mulligan added that the study's cross-sectional design "mandates caution in drawing conclusions from these associations."

## PIs, glucose, diabetes

Earlier work by researchers at the University of California, San Francisco, documented glucose intolerance and lower insulin-mediated glucose disposal and storage in healthy volunteers taking IDV for just four weeks.[25] Analysis of hepatic glucose metabolism in nine of these volunteers, presented at the 5th Lipodystrophy Workshop by Grace Lee (University of California, San Diego), showed that a month of IDV moderately boosts fasting glucose production by the liver and blunts insulin-mediated suppression of hepatic glucose output [abstract 7].

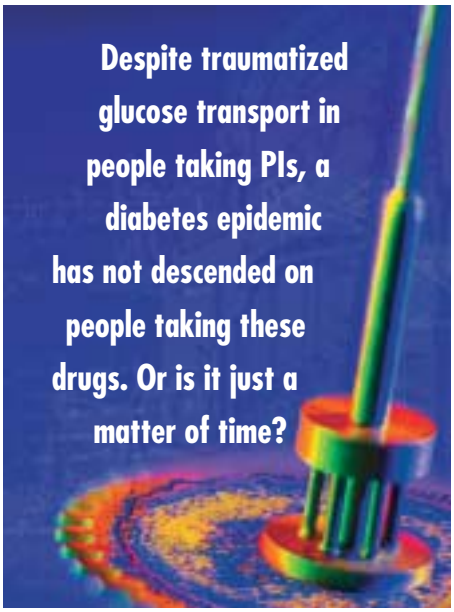
The study used the standard, three-times-daily dose of IDV. Fasting glucose climbed from 4.9 mmol/L at baseline to 5.1 mmol/L after week four, a 7 percent jump that landed just short of statistical significance ($P = 0.06$). Fasting hepatic glucose production rose from 12.6 mmol/kg/min at baseline to 13.5 mmol/kg/min after week four ($P < 0.03$). Over the same period, fasting insulin bolted from 62.1 pmol/L to 80.7 pmol/L ($P = 0.055$). HOMA-calculated insulin resistance increased significantly. Insulin's ability to suppress glycogenolysis and gluconeogenesis waned after treatment with IDV.

Once PI therapy unglues glucose metabolism, patching things up takes time. Even after 96 weeks without PIs, glucose metabolism improves only "modestly," 5th Lipodystrophy Workshop attendees learned from Marc van der Valk (International Antiviral Therapy Evaluation Center, Amsterdam) [abstract 8]. Sidelining PIs did yield slow improvements in subcutaneous and visceral adipose tissue.

The study involved eight men with severe lipoatrophy who traded their PIs for ABC without losing viral control for 96 weeks. Van der Valk chalked up these changes after 96 weeks of non-PI treatment:

- During fasting, total glucose production dropped from 16.1 ± 2.5 µmol/kg/min at baseline to 15.0 ± 1.6 µmol/kg/min.
- During fasting, glucose oxidation as a percent of total glucose disposal rose from 30.5 ± 10.4 percent at baseline to 48.8 ± 15.6 percent.
- During insulin infusion, neither endogenous glucose production nor total glucose disposal changed after PI withdrawal, but again glucose oxidation improved.
- Fasting glycerol, a measure of lipolysis, dropped from 2.6 ± 0.6 µmol/kg/min at baseline to 1.8 ± 0.3 µmol/kg/min at week 96.
- Subcutaneous adipose tissue increased by 10 $cm^2$, and visceral adipose tissue decreased by 38 $cm^2$.

Reviewing this study at the 2nd IAS Conference,[13] van der Valk's collaborator Peter Reiss spelled out the bottom line: Modestly improved glucose production and lipolysis did not approach levels seen in healthy volunteers after 96 weeks without PI therapy, a result "suggesting persistence of insulin resistance both in adipose tissue and muscle or in the liver."




Earlier work blamed PI inhibition of the glucose transporter GLUT4 for insulin resistance during PI therapy.[26] The sluggish improvement in glucose metabolism charted by van der Valk led him to suggest PIs may permanently damage GLUT4. "Something must be broken," he proposed. An alternative hypothesis, mentioned in his study abstract, is that PIs gum up other (or additional) go-betweens that insulin exploits to regulate glucose. Grace Lee endorsed this second option, noting that IDV's effects in her study cannot be explained by GLUT4 alone.

Despite traumatized glucose transport in people taking PIs, a diabetes epidemic has not descended on people taking these drugs. Or is it just a matter of time? A comparison of 288 men without HIV infection and 339 infected men in the Multicenter AIDS Cohort Study (MACS) logged a higher incidence of "pre-diabetes" (hyperglycemia) and of diabetes itself in antiretroviral-treated men [abstract 43]. The incidence of hyperglycemia (fasting glucose between 110 and 125 mg/dL) or diabetes (fasting glucose 126 mg/dL or higher) proved highest among men taking antiretrovirals, lower in the HIV-seronegative group, and lowest in an HIV-infected group not taking antiretrovirals.

The analysis included men with an initial fasting glucose at or below 105 mg/dL and no history of diabetes. Todd Brown (Johns Hopkins University, Baltimore) reckoned the overall incidence of hyperglycemia at 6.6 cases per 100 person-years and the diabetes incidence at 2.5 cases per 100 person-years (Table 5). Compared with the uninfected men, the antiretroviral-treated group had a 40 percent higher chance of hyperglycemia and a 71 percent higher chance of diabetes.

When Brown determined the risk of hyperglycemia or diabetes according to specific drugs, he found the highest risk among people taking ddI/d4T or EFV. Compared with the uninfected group, hazard ratios adjusted for age, body mass index, and alcohol intake measured 1.3 for any PI, 1.38 for any antiretroviral regimen, 1.48 for d4T, 2.31 for EFV, and 2.55 for ddI/d4T. The MACS team counted 11 diagnoses in people taking EFV and 24 in people taking any PI, but it was unclear if some of those taking EFV had just switched to the nonnuke after running into trouble with a PI. Earlier studies did not find that EFV causes hyperglycemia or insulin resistance. Brown noted that the study may underestimate the overall incidence of high glucose and diabetes in people taking antiretrovirals because everyone's first visit came during or after April 1999, three years into the HAART era.

## PIs, adiponectin, arteries

The healthful hormone adiponectin enthralls lipodystrophy mavens because it plays roles in two arenas where PIs also perform—the circulatory system and glucose metabolism. On top of that, as its name implies, adiponectin comes from fat cells. So when fat cells vanish, as they do in people with lipoatrophy, adiponectin levels fall. A cottage industry of adiponectin research in people with HIV has already cranked out the following findings:

1. HIV-infected people with lipodystrophy have lower adiponectin levels in blood than HIV-infected people without lipodystrophy.[27-32]

**Table 5. Incident hyperglycemia and diabetes in the MACS cohort**

| | | *Person-years (p-y)* | *Rate/100 p-y* | *Hazard ratio** |
|---|---|---|---|---|
| Hyperglycemia | Overall | 1,074.7 | 6.6 | |
| | HIV-uninfected | 480.2 | 7.3 | 1 |
| | HIV with no treatment | 174.3 | 2.9 | — |
| | HIV with treatment | 420.2 | 7.4 | 1.4 |
| Diabetes | Overall | 1,109.6 | 2.5 | |
| | HIV-uninfected | 501.7 | 2.4 | 1 |
| | HIV with no treatment | 177.2 | 1.1 | — |
| | HIV with treatment | 430.7 | 3.3 | 1.71 |

*Adjusted for age, body mass index, and alcohol intake.
Source: Todd Brown, abstract 43.

2. HIV-infected people with lipodystrophy have lower adiponectin levels in subcutaneous fat than HIV-infected people without lipodystrophy.[29]
3. HIV-infected people with more limb fat have more adiponectin in their blood.[27,31,32] [and abstract 12]
4. Higher adiponectin levels correlate with insulin sensitivity.[27,28,30,32,33]
5. Lower adiponectin levels correlate with insulin resistance.[29,31]
6. Lower adiponectin levels correlate with high cholesterol and triglycerides.[30,33]
7. Higher adiponectin levels correlate with higher high-density lipoprotein cholesterol.[30,31]
8. Lower adiponectin levels correlate with use of NRTIs.[31]

The consistency of these findings from one cross-sectional study to the next clearly implies, as one team writes, that "changes in adiponectin may contribute to the metabolic dysregulation" in people with HIV lipodystrophy.[30] Researchers at Boston's Brigham and Women's Hospital propose that "NRTI use may worsen insulin resistance by decreasing adiponectin levels."[31] And, perhaps inevitably, people have started pondering adiponectin replacement therapy as "a potential treatment option to ameliorate the metabolic changes observed in this patient population."[31]

But some people taking antiretrovirals may already be pumping up their adiponectin payloads—to compensate for PI-induced endothelial dysfunction. That unexpected possibility came to light in a four-week study of 10 healthy, nonobese volunteers without HIV infection or hypertension [abstract 1]. Because earlier work tied PIs to impaired endothelial function,[34] Sudha Shankar (Indiana University, Indianapolis) gauged leg blood flow after infusion of methacholine before and after four weeks of thrice-daily IDV. A blood flow surge in response to methacholine means the endothelium and vascular smooth muscle have not lost their elasticity. Decreased blood flow means damage.

Shankar found that adiponectin levels rose 30 percent, from 14.2 to 18.4 µg/mL, after four weeks of IDV ($P < 0.05$). At the same time, as in other PI studies, HOMA-measured insulin resistance worsened ($P < 0.05$). And leg blood flow ebbed by 60 percent from the baseline measure to week four ($P < 0.01$). This decreased flow correlated with increased adiponectin ($r = 0.853$, $P < 0.005$), and increased adiponectin correlated with the degree of endothelial dysfunction ($r^2 = 0.585$, $P < 0.05$).

What does it all mean? The jump in adiponectin, Shankar suggested, may be the body's way of fighting back after endothelial damage. Animal studies show that adiponectin lessens the neointimal thickening and vascular smooth muscle proliferation that result from vascular damage. So, strange as it may sound, IDV-induced endothelial damage may protect people from even worse insulin resistance by boosting adiponectin levels—though mauling your endothelium is probably not the best way to ward off diabetes. Shankar did not suggest the other, even more bizarre, corollary: Indinavir-induced jumps in adiponectin may ameliorate the metabolic and morphologic mix-ups tied to antiretrovirals.

Of course it's way too early to read much meaning into this intriguing experiment. Shankar noted that the study does not prove that adiponectin levels rose in response to vascular damage, only that the two correlate. The adiponectin uptick could be a direct result of IDV, she suggested, or some other mechanism may be involved. And whether other PIs have the same effect remains to be seen.

Another study of blood vessels in people taking antiretrovirals yielded another uncanny result: After 12 months of antiretroviral therapy, carotid intima media thickness—a harbinger of atherosclerosis—increased most in people who started the study with the highest CD4 counts [abstract 2]. Perhaps, suggested Patrick Mercié (University Hospital, Bordeaux), treatment-induced immune restoration takes a toll on the arteries. A player in this plot may be CD40 ligand, "which is widely implicated in the progression of atherosclerosis" and which CD4 cells spew.

The study involved 346 members of the Aquitaine cohort who had ultrasonography to gauge intima media thickness two times, 12 months apart. Mean thickness inched significantly upward from 0.57 mm at month 0 to 0.59 mm at month 12 ($P < 0.0001$). Those measures fall within the normal range for the general population.

The increase correlated with several classic cardiovascular risk factors—older age ($P < 0.0001$), male gender ($P = 0.02$), and smoking ($P = 0.05$). But were the cohort's carotid arteries narrowing just because they were getting older and smoking too much (70 percent smoked at month 12)? Or did their high CD4 counts (447 cells/mm$^3$ at baseline and 490 cells/mm$^3$ at month 12) have more to do with it? The baseline CD4 count, Mercié found, was the only variable that correlated independently with thicker intima media at month 12 ($P = 0.0145$). Splitting the cohort into baseline CD4 quartiles, he charted dramatically higher intima media thickening from the first through the third quartile (Table 6).

These findings offer an interesting contrast with a study of 148 people with HIV infection, 79 of them tracked for one year [abstract 35]. Priscilla Hsue (University of California, San Francisco) reported two striking differences from Mercié's findings:

- Mean intima media thickness at baseline measured 0.90 mm, far above the normal 0.57 mm in the Aquitaine cohort.
- The average thickness increased 0.1 mm per year, 5 times the one-year gain in the French study.

But a third finding by Hsue may reflect one of Mercié's results: A nadir CD4

**Table 6. Higher CD4 counts correlate with thickening artery walls**

| *Baseline CD4 quartile (cells/mm³)* | *Month 12 increase in IMT (µm)* |
|---|---|
| 3 to 253 | 1.98 |
| 253 to 402 | 10.17 |
| 402 to 590 | 42.67 |
| 590 to 2,270 | 27.73 |

IMT = carotid intima media thickness.
Source: Patrick Mercié, abstract 2.

count at or below 200 cells/mm$^3$ correlated with thicker artery walls at baseline ($P = 0.072$) and with the one-year progression rate ($P = 0.049$). The median nadir in the group measured 110 cells/mm$^3$, and they had been taking a PI regimen for a median of 3.3 years. At that point the median CD4 count had climbed to 354 cells/mm$^3$. So the immune restoration mechanism proposed by Mercié could also be at work in Hsue's cohort. But the gain from nadir to baseline CD4 count did not predict intima media thickness in Hsue's analysis. Instead she stressed the chronic inflammation of untreated HIV infection—reflected in the low CD4 nadirs—as a potential explanation of the thickening artery walls.

Why did Hsue measure much thicker artery linings at baseline, and much faster progression over one year, than Mercié did? Smoking is not the answer, because 64 percent of the Aquitaine cohort smoked at baseline compared with 56 percent of Hsue's group. Neither is age, with a median of 45 years in Hsue's cohort and a mean of 42 in Mercié's.

So other factors must explain these differences. Hsue reported that 34 people (23 percent) had hypertension, and eight (5 percent) already had coronary artery disease. Mercié did not report vascular disease rates in his cohort. Smoking ($P = 0.001$) and hypertension ($P = 0.091$) correlated with baseline intima media thickness in a multivariate analysis by Hsue, as did being Latino (which usually means Mexican in California) ($P = 0.047$). Mercié did not define the ethnic breakdown of his cohort, though it probably included few if any Mexicans.

But the most important difference between the studies probably lies in the methods used to gauge artery wall thickness. Aquitane researchers measured only common carotid intima media thickness, whereas Hsue measured 12 segments—six on the left and six on the right. "We find the majority of disease in the bifurcation of the common carotid into the external and internal carotid arteries," Hsue wrote to *IAPAC Monthly*. "This would be missed if one only measured one segment of the vessel." That difference could explain both the higher baseline thickness in Hsue's study and the faster progression.

Other variables that independently correlated with baseline intima media thickness in Hsue's study were older age ($P < 0.001$), higher low-density lipoprotein cholesterol ($P = 0.002$), and (as already noted) nadir CD4 count at or below 200 cells/mm$^3$ ($P = 0.072$). When Hsue rated predictors in an analysis that included 63 gender- and age-matched seronegative controls, HIV infection also independently predicted narrower carotids ($P = 0.001$). Compared with controls, the HIV group had significantly more intima media thickening at baseline ($P = 0.0001$), even though the median baseline thickness of Hsue's control group was well above the 12-month thickness in Mercié's HIV group (0.70 mm versus 0.59 mm).

In a multivariate analysis of one-year intima media thickness progression, Hsue found three independent predictors: older age ($P = 0.01$), being Latino ($P = 0.024$), and CD4 nadir ($P = 0.049$).

## Atazanavir, lopinavir, lipids, lipodystrophy

A metabolic substudy of the international trial comparing atazanavir (ATV) with EFV (plus AZT/3TC) in treatment-naive people found similar rates of fat changes in the two treatment groups after 48 weeks [abstract 14]. Joseph Jemsek (Jemsek Clinic, Huntersville, North Carolina) reported that 111 people taking ATV and 100 taking EFV had modest fat gains in all body compartments. While average weight rose 1.2 kg, three ratios of fat distribution did not change significantly with either regimen through 48 weeks—visceral-to-total adipose tissue, visceral-to-subcutaneous adipose tissue, and subcutaneous-to-total adipose tissue. Noting that body fat differences between groups taking EFV or NFV in ACTG 5005 did not appear until week 80, Michael Dubé (Indiana University, Indianapolis) suggested that follow-up in the ATV study may be too short to support conclusions.

Analysis of two trials comparing ATV with LPV in PI-experienced people confirmed the sleek lipid profile of ATV [abstract 119]. In a study pitting standard-dose LPV against 400 mg of ATV once daily for 24 weeks, mean low-density lipoprotein (LDL) cholesterol rose 5 percent with LPV while falling 6 percent with ATV ($P < 0.05$). Triglycerides soared by a mean 56 percent in the LPV arm while falling 2 percent with ATV ($P < 0.0001$). In the second 24-week study, comparing three PI rescue regimens after triple-class failure, triglycerides climbed 31 percent with LPV while falling 2 percent with ATV/RTV (300/100 mg once daily) and falling 14 percent with ATV/SQV (400/1,200 mg once daily) ($P < 0.0001$).

More interesting than the comparison of ATV with LPV was the comparison of unboosted ATV (400 mg once daily) with RTV-boosted ATV (300/100 mg once daily) in the two studies. Kenneth Lichtenstein (University of Colorado, Denver) reported that both regimens effectively lowered total cholesterol, LDL cholesterol, and triglycerides (Table 7). Because trough levels of unboosted ATV can fall dangerously low in some people,[35] more than one expert has asked whether ATV should *always* be boosted, regardless of whether a person is taking the drug as a first PI or in a backup regimen. Since 100 mg of RTV appears not to mar ATV's limpid lipid record, that argument sounds sensible.

Abbott researchers led by Scott Brun fed body fat data from four LPV trials into a Cox proportional hazard model to isolate risk factors for fat gains and losses through 96 weeks of treatment [abstract 99]. Four independent predictors emerged:

- Caucasian, non-Hispanic: hazard ratio (HR) 2.14, $P = 0.001$
- Age (per year increase): HR 1.04, $P < 0.001$
- Baseline glucose (per 10 mg/dL increase): HR 1.06, $P = 0.039$
- Current alcohol use: HR 1.74, $P = 0.025$

Among the factors that did not favor lipodystrophy were male gender, baseline weight, baseline lipids or lipid gains, baseline CD4 count, smoking, and hypertension.

**Table 7. Lipids with unboosted versus boosted ATV**

| | *Unboosted ATV (400 mg once daily)* | *ATZ/RTV (300/100 mg once daily)* |
|---|---|---|
| Percent with total cholesterol ≥200 mg/dL | Baseline: 32 percent<br>Week 24: 19 percent | Baseline: 41 percent<br>Week 24: 21 percent |
| Percent with LDL cholesterol ≥250 mg/dL | Baseline: 24 percent<br>Week 24: 11 percent | Baseline: 28 percent<br>Week 24: 15 percent |
| Percent with triglycerides ≥250 mg/dL | Baseline: 21 percent<br>Week 24: 19 percent | Baseline: 26 percent<br>Week 24: 22 percent |

Source: Kenneth Lichtenstein, abstract 119.

### Safety skirmishes: efavirenz versus nevirapine

The choice between EFV and NVP as first-line therapy rests only partly on how one interprets the conflicting efficacy data.[36-40] Equally important is the relative safety of these drugs. Two reports at the 5th Lipodystrophy Workshop reached divergent conclusions about nonnucleoside toxicity, but a third report at the 2nd IAS Conference saw more merit in EFV.

A EuroSIDA study of 1,738 people starting NVP and 1,635 starting EFV found that a higher proportion stopped NVP, usually because of toxicity [abstract 24]. Liver failure proved uncommon with either drug. Nina Friis-Møller (Hvidovre University Hospital, Denmark) reported several factors that may have favored EFV in this analysis. The EFV group had a significantly lower median viral load (3.4 logs versus 3.8 logs with NVP, $P = 0.0001$) and a higher CD4 count (319 cells/mm$^3$ versus 288 cells/mm$^3$ with NVP, $P = 0.004$). Significantly more people starting EFV had taken no earlier antiretrovirals, though the proportion of naive people was small in each group (6.7 percent for EFV and 3.7 percent for NVP, $P = 0.006$).

Time to stopping a nonnucleoside for any reason proved significantly shorter with NVP ($P < 0.0001$). After 40 months of follow-up, about 60 percent wanted no more NVP and about 50 percent forsook EFV. In the first month of treatment, more people stopped NVP because of rash, and more stopped EFV because of central nervous system side effects ($P < 0.05$ for both comparisons). After 12 months of therapy, dyslipidemia accounted for about 5 percent of EFV withdrawals and central nervous system toxicity about 10 percent, both significantly more than with NVP ($P < 0.05$). But after a year of treatment, NVP had failed virologically in about 50 percent compared with about 35 percent taking EFV ($P < 0.05$).

About 6 percent abandoned NVP because of liver toxicity versus about 3 percent for EFV, but that difference lacked statistical significance. The incidence of liver failure proved nonsignificantly higher with EFV—0.49 per 100 person-years (95 percent confidence interval [CI] 0.19 to 0.86) versus 0.29 per 100 person-years (95 percent CI 0.11 to 0.62) with NVP. More people taking NVP than taking EFV had HCV coinfection (85.7 versus 77.8 percent) or hepatitis B virus (HBV) coinfection (37.5 versus 22.2 percent).

A much smaller study, involving 249 people taking EFV and 165 taking NVP at Madrid's 12 de Octubre Hospital, counted more safety failures with EFV [abstract 141]. As in the EuroSIDA study, a significantly higher proportion started EFV as part of their first regimen (22 percent versus 10 percent with NVP, $P < 0.001$). But Miguel Torralba reported no other baseline differences between the groups.

Although rash proved more common with NVP, the difference from EFV was not significant (15.3 percent versus 12.5 percent). But a higher NVP-linked incidence of grade 3 or 4 rash approached significance (6.1 percent versus 2.4 percent with EFV, $P = 0.059$), and a significantly higher proportion stopped NVP because of rash (11.5 percent versus 5.8 percent, $P = 0.044$). Eighty-four people taking EFV had central nervous system toxicity, and 35 of them (42 percent) dumped the drug as a result. A Cox regression analysis did not link NVP to higher rates of hepatotoxicity, after controlling for HCV, HBV, gender, age, use of RTV, CD4 count, and viral load.

The overall discontinuation rate measured 29 percent with EFV and 20 percent with NVP after one year of follow-up, though this difference lacked statistical significance ($P = 0.101$). But in another Cox analysis, after adjustment for age, gender, HCV, HBV, number of antiretrovirals, use of RTV, CD4 count, and viral load, people were 1.66 times more likely to quit EFV than NVP ($P = 0.034$). One factor that may explain the difference between these two studies is the high proportion of injecting drug users among Spanish people with HIV compared with the larger European population represented by EuroSIDA. Drug users could be more sensitive than others to the central nervous system insults of EFV.

A third cohort study, reported by Chelsea and Westminster Hospital's Gail Matthews at the 2nd IAS Conference, mirrored the EuroSIDA finding that more people dropped NVP sooner than EFV.[41] Unlike the two cohorts reported at the 5th Lipodystrophy Workshop, the London group consisted entirely of treatment-naive people starting either EFV or NVP. After 292 patient-years of follow-up, 35 of 287 (12 percent) taking NVP had to switch because of toxicity, compared with 22 of 328 taking EFV (7 percent). Kaplan-Meier analyses graphed a longer time to virologic failure ($P = 0.003$) and a longer time to virologic plus toxicity failure ($P = 0.0324$) with EFV.

Although the two groups did not differ in gender, proportions with an AIDS diagnosis, or baseline CD4 count or viral load, the NVP group tended to take ddI/d4T, while the EFV group usually opted for AZT/3TC. And in a multivariate analysis, ddI/d4T raised the risk of failure 1.92 times ($P = 0.008$). Starting with EFV lowered the failure risk 40 percent ($P = 0.012$). Switching only NRTIs did not count as a regimen failure in Matthews' analysis, but she noted that some people ditching the d-drugs because of toxicity may have dumped NVP at the same time.

## FOUCAULT'S PENDULUM

Leptin was the watchword at last year's Lipodystrophy Workshop; this year leptin's cytokine cousin adiponectin took its turn in the spotlight. Early evidence shows that these two agents straddle mechanistic pathways to miscarried metabolics. But whether low levels of leptin or

adiponectin are cause or consequence of specific disorders is not always clear. And whether fiddling with levels of these hormones can ease lipodystrophy and related problems remains an even tougher call.

Despite these many unknowns (and the merely jocular suggestion of this article's subtitle), no one really thinks HIV researchers should forget adiponectin in the struggle to understand fat morphs and metabolic meanderings. But neither did anyone inflate hopes about therapeutic prospects for leptin or adiponectin replacement when certain simpler tactics can be tried today—and when some of them will certainly help ease the toxicities considered at this 5th Lipodystrophy Workshop. Like exercising, and stopping smoking, and screening women with HIV for osteoporosis.

Such tactics can be called Foucaultian in their humble, nearly hit-yourself-in-the-head transparency. Just set that big pendulum swinging, stand around for a few hours, and watch the world wag. This view of clinical research does not mean that any good study is easy in its conception, planning, or execution. What most impresses about Foucault's pendulum is not how painfully obvious it seemed in the end, but how this elegant proof eluded all until Foucault had the thought, planned the experiment, and got it done.

So here are some nominations for the Order of Jean-Bernard-Léon Foucault, bestowed on those who uncover antitoxicity tactics that sound obvious but remain obscure until someone does the work.

*1. Manage PI-induced diarrhea with measures that work for other diarrhea.*

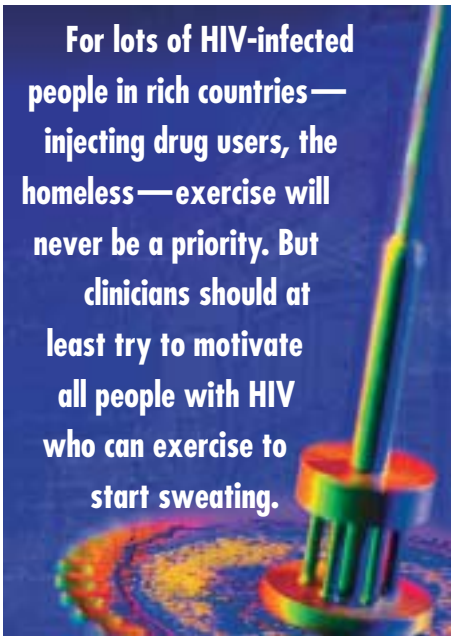
"A straightforward, effective way to resolve [PI-induced] diarrhea and promote gut health is necessary," suggest Carla Heiser (Indiana University, Chicago) and colleagues at other sites [abstract 105]. Now who would argue with that? Yet NFV has been on the market for six years, and the main pre-Heiser help proffered was Imodium (loperamide).

Heiser randomized 28 people to dietary supplementation and seven to standard of care. In the intervention group, 22 were taking NFV and six LPV. All study participants had noticeable fat redistribution and two of the following seven problems: diarrhea despite loperamide, more than two episodes of watery or loose stools daily, total cholesterol above 200 mg/dL, LDL cholesterol above 130 mg/dL, triglycerides above 200 mg/dL, fasting glucose above 115 mg/dL twice, insulin above 20 mIU/L. In the treatment group, only one person qualified for the study because of hyperlipidemia.

The dietary regimen included two or three courses:

- Acidophilus and bifidobacteria, 1.2 g each morning on an empty stomach
- Soluble fiber, 11 g two hours after antiretrovirals
- If diarrhea persists at week four: L-glutamine, 10 g daily increased weekly to 30 g daily

Diarrhea resolved completely in 13 of 28 people after four weeks of treatment. Adding L-glutamine reduced diarrhea in 11 of the remaining 15 people by week 12 (Table 8). At the end of the study, Heiser reported, participants "were highly motivated to continue with these simple strategies."




*Honorable mention:* At the 2nd IAS Conference, Canadian researchers reported some success in treating NFV-induced diarrhea with different combinations of fiber (psyllium), loperamide, and calcium carbonate.[42] In a study not covered by this reporter, 18 people took 1,250 mg of calcium carbonate twice daily. If that didn't help within 48 hours, they doubled the dose. After nine weeks the average number of bowel movements dropped from three to two daily, and diarrhea decreased significantly. A full report of this study is online.[43]

*2. Get people with wide waists and insulin resistance to exercise.*

A randomized study of 37 people with fat redistribution and hyperinsulinemia showed that exercise plus metformin outdoes metformin alone in correcting insulin imbalances and trimming central fat [abstract 4]. As a bonus, strength and aerobic capacity improved in the exercise group.

Susan Driscoll (Massachusetts General Hospital, Boston) randomized 18 people to take metformin at a dose of 850 mg twice daily and 19 to take metformin and start a supervised exercise program. Men had a waist-to-hip ratio above 0.9 and women a ratio above 0.85. The exercise group kept food diaries to ensure that their diets didn't change after they started to work out. For 12 weeks they completed three weekly exercise sessions consisting of 30 minutes of aerobic activity at 75 percent of maximum capacity and three sets of 10 resistance repetitions at 80 percent of the maximum weight wielded in a single repetition.

This regimen proved too taxing for some. Eight people dropped out of the exercise arm, most because they couldn't keep up with the workout schedule. Four people quit the metformin-only arm. One person in each group had a mild increase in lactates, a side effect of metformin. Among people who completed the three-month study, strength and aerobic capacity surged in the exercise-metformin group compared with the metformin-alone group ($P = 0.045$). People who exercised also enjoyed significant improvements in:

- Waist-to-hip ratio (-0.02 versus -0.01 with metformin alone, $P = 0.026$)
- Abdominal fat (-13 cm versus -1 cm with metformin alone, $P = 0.049$)
- Systolic blood pressure (-12 mm Hg versus 0 mm Hg with metformin alone, $P = 0.012$)
- Diastolic blood pressure (-10 mm Hg versus 0 mm Hg with metformin alone, $P = 0.001$)
- Fasting insulin ($P = 0.03$)
- Insulin area under the curve ($P = 0.043$)

Several small studies establish that aerobic or resistance exercise can cut total or central fat,[44-46] along with triglycerides[45,47] and cholesterol[45] in people with HIV infection. As Driscoll and other workers[48] show, it also helps get glucose metabolism clicking again. IAS-USA guideline writers

**Table 8. Response to 12 weeks of dietary supplements for diarrhea**

| | *Baseline (mean ± SD)* | *Week 12 (mean ± SD)* | *P* |
|---|---|---|---|
| Diarrhea (self-reported episodes/day) | 2.84 ± 1.42 | 0.74 ± 1.05 | <0.0001 |
| Loperamide use (mg/day) | 3.67 ± 3.93 | 0.57 ± 1.03 | <0.001 |
| Stool frequency (number/day) | 3.4 ± 1.25 | 2.54 ± 1.34 | 0.0007 |

Source: Carla Heiser, abstract 105.

**Table 9. Smoking and aging team up to raise CHD rates***

| | *Nonsmokers* | | *<10 Cigarettes/day* | | *>10 Cigarettes/day* | |
|---|---|---|---|---|---|---|
| *Age (y)* | *n* | *Rate/1,000 person-years* | *n* | *Rate/1,000 person-years* | *n* | *Rate/1,000 person years* |
| 18 to 25 | 14 | 0.0 | 16 | 0.0 | 18 | 0.0 |
| 25 to 35 | 132 | 2.2 | 97 | 0.0 | 206 | 3.0 |
| 35 to 45 | 150 | 0.0 | 28 | 0.0 | 201 | 10.2 |
| 45+ | 129 | 0.0 | 69 | 43.5 | 48 | 43.8 |

*Incidence of coronary heart disease (CHD) and peripheral arterial disease in 1,281 people taking a PI regimen.
Source: Geneviève Chêne, abstract 34.

recommend resistance training to ward off bone loss.[9] For people taking antiretrovirals, the only apparent drawback of aerobic exercise is the risk that subcutaneous fat may fade faster.[46]

For lots of HIV-infected people in rich countries—injecting drug users, the homeless—exercise will never be a priority. But clinicians should at least try to motivate all people with HIV who can exercise to start sweating. As two New York teams showed, workout routines are feasible even among poor inner-city dwellers.[49,50]

*3. Nag people to stop smoking.*

Cigarette smoking turned up on the wrong side of the risk ledger in multivariate analyses from several 5th Lipodystrophy Workshop studies. Lighting up independently predicted lower leg fat in American women with HIV infection [abstract 15 above] and signaled thicker carotid artery walls in French and US populations [abstracts 2 and 35 above]. But the biggest indictment of tobacco came from APROCO cohort investigators, who found a nearly negligible rate of new cardiovascular disease in PI takers who didn't smoke [abstract 34].

Besides smoking, the only other variable that raised the risk of heart disease in these 1,281 people is a problem no one can correct—getting older. Eight other factors in a Poisson regression model didn't matter: body mass index, gender, CD4 count, viral load, PI prescribed, dual NRTIs prescribed, alcohol consumption, and cannabis consumption. Indeed, reported Geneviève Chêne (INSERM U593, Bordeaux), cannabis connoisseurs had a nonsignificantly lower rate of cardiovascular disease (3.2 per 1,000 person-years, 95 percent confidence interval [CI] 0 to 7.7) than people who never inhaled the stuff (6.2, 95 percent CI 3.2 to 9.3).

From May 1997 through March 2003, Chêne counted 28 cardiovascular "events" (18 of them coronary heart disease) in 22 people for an incidence of 5.3 per 1,000 person-years (95 percent CI 3.0 to 7.3). Comparing people who smoked more than 10 cigarettes a day with those who smoked fewer than 10 and those who smoked none, she figured the following rates per 1,000 person-years and 95 percent CIs ($P = 0.003$):

- More than 10 cigarettes a day: 10.3 (5.2 to 15.3)
- Fewer than 10 cigarettes a day: 5.6 (0 to 11.1)
- Nonsmokers: 0.7 (0 to 2.0)

Only one nonsmoker had a new heart disease diagnosis. Among light and heavy smokers, the incidence of new diagnoses rose with advancing age (Table 9). Given these results, one might countenance a blunter conclusion than Chêne's suggestion that "smoking cessation should be seriously considered" in PI takers.

*4. Watch for preeclampsia in pregnant women taking triple therapy.*

Preeclampsia (pregnancy-induced hypertension and proteinuria) and stillbirths proved more common among antiretroviral-treated women at Barcelona's University Hospital Clinic than among pregnant women not infected with HIV [abstract 22]. Among the 71 women with HIV, 61 were taking a three-drug regimen, while seven others were taking one or two antiretrovirals. In the past two years, Oriol Coll and collaborators began treating HIV-infected pregnant women during all three trimesters. Coll suggested that if others confirm the heightened risk of preeclampsia and stillbirths with potent antiretroviral therapy, clinicians may want to reconsider antiretroviral recommendations for pregnant women.

The study involved all 7,720 pregnant women who delivered a child at the University Hospital Clinic from January 2001 through March 2003. Coll reported 104 cases of preeclampsia (1.3 percent) and 53 stillbirths (0.7 percent). The relative risk (RR) of both proved much higher among women with HIV than in the uninfected women:

- Preeclampsia: 12.7 percent with HIV versus 1.2 percent without HIV, RR 11.54
- Stillbirth: 5.6 percent with HIV versus 0.6 percent without HIV, RR 17.32

A preliminary analysis suggested a correlation between AZT (but no other individual antiretroviral) and preeclampsia or stillbirth, Coll added. But the correlation may just reflect frequent use of prophylactic AZT among pregnant women with HIV infection.

*5. Screen HIV-infected women for osteoporosis.*

All women risk waning bone mineral density as they pass menopause, and dwindling bone density poses a threat to everyone with HIV infection. So no one professed surprise when two recent studies charted high rates of osteopenia and osteoporosis in HIV-infected women.[51,52] A comparison of 84 women with HIV and 63 age-, weight-, and race-matched controls confirmed the threat of weakening bones in women with HIV so strongly that routine screening of older or at-risk HIV-infected women seemed to many an inescapable conclusion [abstract 23].

**Table 10. Osteopenia and osteoporosis in women with HIV and uninfected controls**

| | *Osteopenia* | | *Osteopenia or osteoporosis* | | |
|---|---|---|---|---|---|
| | *HIV+ (%)* | *Controls (%)* | *HIV+ (%)* | *Controls (%)* | *P** |
| Lumbar spine | 28 | 14 | 34 | 19 | ≤0.05 |
| Femoral neck | 33 | 17 | 33 | 19 | NS |
| Total hip | 27 | 8 | 28 | 8 | ≤0.05 |
| Hip or spine | 54 | 30 | 55 | 30 | ≤0.05 |

**P* for comparison of percent with osteopenia or osteoporosis.
Source: Steven Grinspoon, abstract 23.

**Table 11. Annual bone density changes in children with and without HIV**

| *Bone mineral density** | *Children with HIV* | *Healthy controls* | *P* |
|---|---|---|---|
| Lumbar spine (g/cm$^2$) | 0.069 (0.01) | 0.055 (0.003) | 0.17 |
| Total body (g/cm$^2$) | 0.016 (0.007) | 0.035 (0.002) | 0.0038 |
| Arms (g/cm$^2$) | 0.014 (0.004) | 0.032 (0.001) | 0.0004 |
| Legs (g/cm$^2$) | 0.05 (0.013) | 0.054 (0.002) | 0.81 |

*Mean (and standard error).
Source: Alessandra Viganò, abstract 148.

Steven Grinspoon (Massachusetts General Hospital, Boston) reported no significant differences between the HIV group and controls in age (41 ± 1 years in both groups), body mass index (26 and 27 kg/m$^2$), lowest adult weight (57 and 59 kg), endocrine parameters, or daily calcium and vitamin D intake. The study excluded anyone taking a medication or suffering from a condition that would lower bone mineral density, anyone with an opportunistic infection or diabetes, any pregnant women, or anyone taking an anabolic steroid or estrogens.

DEXA-calculated *t* scores of the lumbar spine, total hip, and femoral neck proved significantly lower in the women with HIV than in controls. A significantly higher percentage of HIV-infected women had osteopenia or osteoporosis of the lumbar spine, total hip, and hip or spine (Table 10).

The women with HIV and the controls had similar levels of osteocalcin, a marker of bone formation. But the HIV group had significantly higher levels of urine N-telopeptide, a marker of high bone turnover (39.6 versus 29.2 nM/mM creatinine, $P < 0.05$), and significantly higher levels of osteoprotegerin, which inhibits differentiation of bone-wasting osteoclasts (4.76 versus 3.39 pmol/L, $P < 0.0001$). One would expect high osteoprotegerin quotients to protect against osteopenia. In these women with HIV, Grinspoon suggested, the high levels may indicate a compensatory response to faster bone turnover.

Grinspoon traced positive correlations between lumbar spine density and body mass index ($r = 0.38$, $P = 0.00001$), lowest adult weight ($r = 0.38$, $P < 0.001$), total fat ($r = 0.37$, $P < 0.001$), and total lean mass ($r = 0.4$, $P < 0.001$) and a negative correlation between lumbar spine density and N-telopeptide ($r = -0.28$, $P = 0.01$). In a multivariate analysis controlled for age, body mass index, menstrual function, and race, women with HIV were 2.6 times more likely to have osteopenia than controls (95 percent CI 1.2 to 5.8, $P = 0.02$).

Not one study of antiresorptive therapy found that it didn't work, Grinspoon noted. And there is no reason to assume it won't work in women with HIV infection. To be sure, some early results point in the right direction: A 48-week randomized trial involving 27 men and four women with HIV infection and osteopenia found significantly greater gains in lumbar spine density with alendronate plus vitamin D and calcium than with vitamin D and calcium alone.[53]

Because women with HIV have a magnified risk of osteopenia or osteoporosis, because diagnosis is accurate and noninvasive, and because effective therapy exists, Grinspoon proposed, bone mineral density should probably be measured even in infected women in whom you might not suspect osteopenia, and certainly in women in whom you do suspect it. William Powderly (Washington University, St. Louis) phrased that advice a little differently, saying all HIV-infected women 40 years old or older should be screened for low bone density. No one at the 5th Lipodystrophy Workshop disagreed.

*6. Be aware of slow bone growth in HIV-infected children.*

Women aren't the only HIV-infected people who run a high risk of thin bones. Girls and boys do too. Confirming an earlier study,[54] Alessandra Viganò (L. Sacco Hospital, Milan) learned that children with HIV have significantly lower bone mineral density than healthy children of the same age [abstract 148]. And, unlike adults, children seem not to return toward normal bone densities when treated with potent antiretrovirals.

Viganò's study involved 32 HIV-infected, Caucasian children from 6.3 to 17.7 years old and 381 healthy controls from 5.7 to 19.2 years old. All 32 children with HIV had a viral load below 50 copies/mL and an average CD4 percent of 31.6 percent at baseline and 34 percent after one year of follow-up while taking d4T, 3TC, and a protease inhibitor. None of these children or any controls were taking sex hormones, corticosteroids, vitamin D, or calcium. The controls fell between the third and 97th percentile for anthropometric measures in their age group, none played competitive sports, and none had ever broken a bone.

Compared with controls, at baseline the children with HIV had significantly lower bone mineral density of the lumbar spine (0.083 versus 0.875 g/cm$^2$, $P = 0.001$), arms (0.647 versus 0.655 g/cm$^2$, $P < 0.001$), legs (0.923 versus 0.980 g/cm$^2$, $P < 0.001$), and total body (0.913 versus 0.933 g/cm$^2$, $P < 0.0001$). After one year of continued successful PI therapy, bone density in the children with HIV had not caught up with control bone density for arms, legs, or total body, though it did for the lumbar spine.

When Viganò figured annual changes in bone mineral density, the spinal growth spurt in the HIV group did not differ significantly from the annual change in uninfected controls. Growth rates of leg bone density also proved similar in the two groups. But annual bone growth for children with HIV significantly lagged normal growth in the arms and total body (Table 11).

Viganò proposed two conclusions:

- Children taking successful long-term antiretroviral therapy have deranged bone metabolism.
- HIV-infected children and adolescents seem to be at great risk of not reaching optimal bone mass.

During a 5th Lipodystrophy Workshop discussion of bone mineral density in women with HIV, Perth's David Nolan observed that the most important time to avoid osteopenia is during maximum bone formation—in other words, during childhood and adolescence.

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

## References and Notes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***Editor's Note:*** *Following are selected abstracts from the 5th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, held July 8-11, 2003, in Paris.*

## Abstract 4: Effects of exercise training and metformin on body composition and cardiovascular indices in HIV-infected patients

*SD Driscoll et al.*

*PURPOSE:* Highly active antiretroviral therapy (HAART) is associated with fat redistribution and insulin resistance. Metformin has been shown to improve insulin and select cardiovascular risk markers in this population. Exercise training is known to improve cardiovascular indices among non-HIV patients. Exercise training in combination with metformin may further improve cardiovascular risk indices in comparison to metformin alone among HIV-infected patients. *METHODS:* The investigators conducted a prospective, randomized, three-month study comparing the effects of metformin 850 mg twice daily versus metformin and exercise training in HIV patients on stable HAART, with hyperinsulinemia and/or impaired glucose tolerance, and evidence of fat redistribution (waist-to-hip ratio >0.90 in men and >0.85 in women). Exercise consisted of one hour of aerobic and strength training three times a week. *RESULTS:* Thirty-seven patients were randomized and 25 subjects completed the study. Subjects receiving exercise training and metformin demonstrated significant decreases in median waist-to-hip ratio [-0.02 (-0.06, -0.01) versus -0.01 (0.03, 0.02), $P=0.026$], resting systolic [-12 (-20, -4) versus 0 (-11, 11), $P=0.012$] and diastolic [-10 (-14, -8) versus 0 (-7, 8), $P=0.001$] blood pressures, increased thigh muscle cross-sectional area [3 (-3, 12) versus -7 (-11, 0), $P=0.015$] and improved aerobic capacity (time on exercise bike) [3 (0, 4) versus 0 (-1, 1), $P=0.045$] compared to subjects receiving metformin alone. There were also increases in five out of six strength indices measured by one repetition maximum ($P<0.05$). Fasting insulin and insulin area under the curve (AUC) decreased significantly more in the exercise training and metformin group ($P<0.05$). Lipid and resting lactate did not change significantly between treatment groups. *CONCLUSION:* These data demonstrate that exercise training in combination with metformin significantly improves cardiovascular risk markers more than metformin alone in HIV-infected patients with fat redistribution and hyperinsulinemia. Exercise training was well-tolerated and improved muscle strength and size, as well as aerobic fitness. Combined therapy in selected groups of HIV-infected patients may substantially alter cardiovascular risk.

## Abstract 12: A randomized, double-blind, placebo-controlled study of rosiglitazone for patients with HIV lipodystrophy

*C Hadigan et al.*

*PURPOSE:* Patients treated with antiretroviral therapy often demonstrate loss of subcutaneous fat and metabolic abnormalities, including insulin resistance. The study investigated the effects of rosiglitazone on insulin sensitivity, subcutaneous fat and metabolic indices in patients with HIV lipodystrophy. *METHODS:* The investigators conducted a three-month randomized double-blind placebo-controlled study of rosiglitazone (4 mg/day) in 28 HIV-infected subjects ages 18 to 60 years with hyperinsulinemia and lipoatrophy. Insulin sensitivity was assessed by euglycemic, hyperinsulinaemic clamp and metabolic indices included adiponectin and lipid profile. Body composition assessment included percent body fat and subcutaneous adipose tissue (SAT) area by computerized tomography (CT) scan of the abdomen. After three months, subjects continued on open-label extension with a dose escalation to 8 mg/day for an additional three months. *RESULTS:* Rosiglitazone resulted in improved insulin sensitivity, with increased glucose utilization (+1.7 ± 0.6 vs -0.4 ± 0.5 mg glucose/kg lean body mass/minute, $P<0.02$, mean change ± standard error of measurement [SEM]), increased percent body fat (1.38 ± 0.76 vs -0.91 ± 0.87, $P=0.04$) and adiponectin (2.3 ± 0.6 vs 0.1 ± 0.3 µg/ml, $P<0.01$, rosiglitazone vs placebo, respectively). SAT increased 8 percent ($P=0.01$) with rosiglitazone, but <1 percent with placebo. Self-reported lipoatrophy improved significantly with rosiglitazone ($P=0.03$). Total cholesterol increased with rosiglitazone compared to placebo (mean change +25 ±9 vs -16 ±8 mg/dl, $P<0.01$). With open-label extension, insulin sensitivity remained improved and SAT increased further for a net change of +12 percent from baseline after six months. *CONCLUSION:* These data demonstrate positive effects of rosiglitazone on insulin sensitivity and fat in HIV-infected patients with lipodystrophy and insulin resistance. Thiazolidinediones may provide an important therapeutic benefit. Studies are needed to identify optimal dose, duration of treatment, subpopulations most likely to benefit and choice of specific thiazolidinedione to minimize effects on cholesterol.

## Abstract 15: Trunk fat is conserved with PI-based HAART, but not with non-PI-based HAART, in HIV-infected women in the USA: DEXA sub-study in the Women's Interagency HIV Study

*K Mulligan et al.*

*PURPOSE:* Surveys in HIV-infected men on antiretroviral therapy (ART) consistently demonstrate decreased levels of peripheral fat, but effects on central fat are more variable. It is not known whether similar patterns exist in HIV-infected women, many of whom in the USA are obese. These questions were addressed in a cross-sectional sub-study of fat distribution in the Women's Interagency HIV Study (WIHS), a multicenter cohort study that includes a seronegative group matched for racial demographics and risk factors. *METHODS:* Non-pregnant women underwent whole-body DEXA scanning with standardized regional analysis. Women on hormone replacement or systemic glucocorticoids were excluded. Results were compared in the following groups: HIV-negative (HIV-; n=78), HIV-positive not on ART (HIV+/noART; n=57), HIV-positive on highly active ART with a protease inhibitor (HAART/PI; n=36), and HIV-positive on non-PI containing HAART (HAART/noPI; n=43). Values for regional fat are expressed as g/cm height. Data are mean ±SE. *RESULTS:* The groups were well matched with respect to race (49 and 47 percent African American; 40 and 40 percent Hispanic in HIV-positive and HIV-negative, respectively). HIV-positive women were slightly older (41 ± 1 vs 38 ± 1 years; $P<0.001$). The majority of both HIV-positive and HIV-negative women were overweight, and many were obese (BMI ≥25 kg/m$^2$ in 66 and 75 percent; and ≥30 kg/m$^2$ in 35 and 51 percent in HIV-positive and HIV-negative, respectively). BMI and total and regional fat did not differ significantly between HIV+/noART and HIV-, showing no effect of HIV infection *per se*. Both trunk and leg fat were significantly lower in HAART/noPI (69.2 ± 4.4 and 48.2 ± 4.0 g/cm, respectively) than in both HIV- (94.2 ± 4.5 and 74.8 ± 3.5 g/cm) and HIV+/noART (84.6 ± 5.1 and 68.7 ± 4.4 g/cm); $P<0.001$ comparing HAART/noPI with HIV- for both trunk and leg fat; $P<0.001$ and =0.02 comparing HAART/noPI with HIV+/noART for trunk and leg fat, respectively. In contrast, in HAART/PI, only leg fat (59.3 ± 4.6 g/cm) was significantly lower than HIV- ($P=0.01$); trunk fat (84.5 ± 6.4 g/cm) did not differ significantly from either HIV- or HIV+/noART. *CONCLUSION:* Consistent with reports in men, lower levels of

peripheral (leg) fat are seen in HIV-infected women on HAART, despite the high prevalence of obesity in this population. Conservation of trunk fat appears to be unique to PI-containing HAART.

## Abstract 16: Long-term changes in lipodystrophy after switching from thymidine nucleoside analogs to abacavir

*A Carr et al.*

*PURPOSE:* The MITOX study demonstrated modest (mean 0.39 kg) recovery of limb fat over six months in lipodystrophic adults who replaced thymidine nucleoside analog therapy (stavudine (d4T) 85 percent; zidovudine (ZDV) 15 percent) with abacavir (ABC). This improvement was not clinically evident, however, over this period. The investigators wished to determine whether clinically relevant recovery of lipodystrophy would occur over a longer follow-up period following thymidine analog withdrawal. *METHODS:* Patients enrolled in MITOX were followed beyond the 24 week randomized phase up to 128 weeks. Patients randomized to remain on thymidine analogs were allowed to switch to ABC at week 24. Serial DEXA and CT scans were used to assess changes in subcutaneous and central fat. Analysis was by intention-to-treat using available data. Multiple linear regression methods were used to examine predictors of change in limb fat. *RESULTS:* Of the original 111 patients randomized, 104 had long-term follow-up data, with 74 having imaging data available at week 104 (mean follow-up 102 weeks). The difference between the ABC and ZDV/d4T arms in mean time-weighted change from baseline to last follow-up for total limb fat (kg), visceral adipose tissue ($mm^3$) and whole-body bone mineral density ($g/cm^2$) were: 0.43 (95 percent CI: 0.12-0.75), -4.84 (95 percent CI: -15.22-5.55) and 0.01 (95 percent CI: -0.08 to 0.09), respectively. Lipid and glycemic parameters did not change significantly. At week 104, the mean increase in limb fat in patients who switched to ABC at baseline was 1.26 kg from a baseline of 3.7 kg. Patients who switched to ABC at baseline also reported slightly greater improvement in self-assessed lipodystrophy severity over 72 weeks ($P=0.148$). Multivariate analysis showed that greater increase in limb fat was associated with lower baseline bone mineral density ($P=0.006$), shorter duration of ZDV pre-study ($P=0.024$) and shorter duration of d4T on study ($P=0.004$). *CONCLUSION:* Lipoatrophy continued to improve for two years after switching d4T or ZDV therapy to ABC, although this was not clinically evident in the majority of patients.

## Abstract 18: Subcutaneous fat tissue mitochondrial DNA depletion and adipose toxicity are strongly associated with nucleoside reverse transcriptase inhibitor (NRTI) therapy in HIV-infected patients

*D Nolan et al.*

*PURPOSE:* To examine the pathophysiology of lipoatrophy in subcutaneous adipose tissue among Western Australian HIV cohort participants, focusing particularly on the potential role of nucleoside reverse transcriptase inhibitor (NRTI)-associated mitochondrial toxicity. *METHODS:* The investigators assessed adipocyte mitochondrial DNA (mtDNA) depletion in 92 subcutaneous fat biopsies from 70 HIV-infected individuals and seven healthy controls. Confocal microscopy and immunohistochemistry were also performed on 26 longitudinal samples from 12 patients initiating or switching therapy, to assess changes in tissue morphology and mtDNA-encoded (COX I) and nuclear DNA (nDNA)-encoded (COX IV) mitochondrial proteins. Mixed effects models were utilized for data analysis, adjusting for multiple measurements in individuals. *RESULTS:* Compared with HIV-infected ART-naive controls (n=24, 1,288 copies/cell), median mtDNA copies/cell was reduced by 81 percent in stavudine (d4T) recipients (n=28, 240 copies/cell, $P<0.0001$) and by 44 percent in zidovudine (ZDV) recipients (n=29, 726 copies/cell, $P=0.006$). Regimens without d4T/ZDV (n=11, 1,514 copies/cell) had similar mtDNA levels to controls ($P>0.5$). Significant differences between d4T/lamivudine (3TC) (n=23) and ZDV/3TC (n=28) regimens were also found ($P=0.002$). Commencing/switching NRTI therapy was associated with significant changes in mtDNA levels within two to 12 months in sequential biopsy samples (n=19, 38 biopsies, $P<0.01$). No association between mtDNA levels and use of HIV protease inhibitors was detected ($P=0.6$), and CD4 T-cell counts at the time of biopsy were also similar between NRTI treatment groups ($P=0.9$). Adipose tissue toxicity correlated with mtDNA depletion and was characterized by adipocyte pleiomorphism and mitochondrial proliferation, progressing to adipocyte loss with marked macrophage infiltration and disordered tissue architecture. Lipid-laden macrophages were detected indicating adipocyte apoptosis. In 4/7 biopsies with <300 mtDNA copies/cell, relative depletion of mtDNA-encoded protein COX I was detected. No significant differences were noted between PI-treated and PI-naive biopsy samples. *CONCLUSION:* These data indicate that adipocyte mtDNA depletion and mitochondrial toxicity are prominent in subcutaneous fat samples obtained from NRTI-treated individuals, providing a pathophysiological basis for the observed effects of NRTI choice and duration on lipoatrophy risk.

## Abstract 19: Uridine prevents and treats mtDNA depletion by NRTI pyrimidine analogs and fully restores mitochondrial function

*UA Walker et al.*

*PURPOSE:* To evaluate if uridine may be suitable to prevent and treat nucleoside reverse transcriptase inhibitor (NRTI)-related mitochondrial toxicity. *METHODS:* Human HepG2-hepatocytes were exposed to NRTIs with or without uridine for 25 days. Cell growth, lactate production, intracellular lipids, mitochondrial DNA (mtDNA) and the respiratory chain subunits (mtDNA-encoded: COX II, nucleus-encoded COX IV) were measured. Phenotypic HIV-resistance assays for NRTIs were performed *in vitro* with T-cell and macrophage-tropic HIV strains in the absence of uridine and in its presence (61.5 µM, 185 µM, or 615 µM). Uridine serum levels were followed in individuals for 24 h after a single dose (36 g) of Mitocnol, a new dietary supplement. *RESULTS:* HepG2 cells exposed to zalcitabine (ddC) (177 nM) without uridine developed a severe depletion of mtDNA (to 8 percent) and of COX II (to 8 percent of wild-type levels). Zalcitabine induced a severe reduction of cell proliferation (to 20 percent), a severe intracellular steatosis and an increase of lactate (350 percent of untreated control). Uridine fully normalized cell proliferation, lactate and intracellular lipids by adjusting mtDNA levels to about 65 percent of NRTI-unexposed control cells. These effects were dose-dependent and maximal at 200 µM of uridine. Uridine also rapidly and fully restored cell function despite continued ddC exposure, when added to cells displaying severe mitochondrial dysfunction (177 nM of ddC for 15 days). Similar results were found in HepG2 cells exposed to 36 µM of stavudine (d4T) (a pyrimidine analog), but not with 11.8 µM of didanosine (ddI) (a purine). Uridine also fully abrogated the increase in lactate and all the cell toxicity of zidovudine (ZDV) (7 µM) + lamivudine (3TC) (8 µM) to HepG2 cells. All these observations were statistically significant (ANOVA). All tested concentrations of uridine did not alter the $IC_{50}$ or $IC_{90}$ of the currently licensed NRTIs in HIV resistance assays, suggesting a lack of interference with the intracellular activation, uptake or interaction with HIV reverse transcriptase. Protective uridine levels can be achieved in human serum by oral Mitocnol. Side effects were not noted. *CONCLUSION:* Uridine fully abrogates mitochondrial toxicity by NRTI-pyrimidines in a preventive and therapeutic setting. Uridine does not appear to interfere with the antiretroviral efficacy of NRTIs. Protective levels of uridine can be achieved in humans with Mitocnol, a new dietary supplement.

## Abstract 22: High incidence of preeclampsia in HIV-infected pregnant women receiving antiretroviral therapy

*A Suy et al.*

*PURPOSE:* Preeclampsia was an extremely rare entity in HIV-infected pregnant women until 2002. Investigators detected a high incidence of preeclampsia in HIV-infected pregnant women receiving antiretroviral therapy in 2002 and 2003. Investigators studied the incidence of preeclampsia among HIV-infected women in Hospital Clinic Universitari (Barcelona) over time and compared it with that of non-HIV-infected patients. *METHODS:* Retrospective study of all pregnant women who delivered (at least 22 weeks of gestation) in Hospital Clinic Universitari. HIV-infected women wishing to become pregnant are recommended to follow ART according to current guidelines. HIV serology is routinely offered to all pregnant women unknown to be HIV-infected in Catalonia and ART is provided to those who are HIV-infected according to current guidelines. Cases of preeclampsia (defined by hypertension and proteinuria) were identified from hospital files. Comparisons of the rates of preeclampsia and ante-partum mortality were done between HIV-infected and non-HIV-infected patients. *RESULTS:* Among 7,720 women delivering at the institution, 71 (0.9 percent) were HIV-infected. There were 3,112 deliveries and 3,215 children born in 2001, 3,634 and 3,744 in 2002, and 974 and 1,002 in the first quarter of 2003, respectively. Children born from HIV-infected mothers were 29 (0.9 percent) in 2001, 30 (0.8 percent) in 2002, and 12 (1.2 percent) in 2003. There were 32 (1 percent) women with preeclampsia in 2001, 51 (1.4 percent) in 2002, and 21 (2.1 percent) in 2003. None (0 percent) of the women with preeclampsia in 2001 was HIV-infected, but six (12 percent) were HIV-infected in 2002, and three (14 percent) in 2003. The risk of preeclampsia in HIV-infected women was 19-fold higher than in non-HIV-infected women in 2002 to 2003 (OR 19.5, 95 percent CI 8.3 to 44.6, $P<0.0001$). The ante-partum mortality was 22 women (none HIV-infected) in 2001, 24 (three HIV-infected), and seven (one HIV-infected) in 2003. preeclampsia was the cause of death in all HIV-infected women. The risk of death in HIV-infected women was 17-fold higher than in non-HIV-infected women in 2002 to 2003 (OR 17.3, 95 percent CI 4.9 to 55.3, $P<0.0001$). *CONCLUSION:* An unexpected high rate of preeclampsia has been identified in HIV-infected

pregnant women in the past two years. If this trend is confirmed by other investigators, it may lead to change in current recommendations on pregnancy in HIV-infected women. Studies of risk factors are under way.

## Abstract 23: Reduced bone density in HIV-infected women

*S Grinspoon et al.*

*PURPOSE:* Reduced bone density has been demonstrated among HIV-infected men, yet little is known regarding bone density in the growing population of HIV-infected women. *METHODS:* Investigators performed an observational study of 84 ambulatory HIV-infected females and 63 healthy female control subjects similar in age (41 ± 1 vs 41 ± 1 years, $P=0.83$), BMI (26.0 ±0.6 vs 27.0 ± 0.5 kg/m$^2$, $P=0.44$) and racial background (percent non-Caucasian, 61 vs 51 percent, $P=0.24$, HIV-infected vs control). Bone density and body composition were measured by DEXA and hormonal indices and bone turnover were assessed. *RESULTS:* Bone density was reduced at the lumbar spine [1.02 ± 0.02 vs 1.07 ± 0.02 g/cm$^2$, $P=0.03$ (T scores, -0.62 ± 0.14 vs -0.13 ± 0.14 SD, $P=0.02$)] and total hip [0.93 ± 0.01 vs 0.99 ± 0.01 g/cm$^2$, $P=0.004$ (-0.33 ± 0.11 vs 0.15 ± 0.11 SD, $P=0.003$)] in HIV-infected subjects compared to control subjects. Osteopenia was demonstrated in 54 vs 30 percent, $P=0.004$ and osteoporosis in 10 vs 5 percent HIV-infected vs control, $P=0.27$. 1,25-dihydroxyvitamin D (25.4 ± 2.3 vs 33.8 ± 2.5 pg/ml, $P=0.01$) was reduced, whereas urinary NTx (39.6 ± 3.5 vs 29.9 ± 2.0 nM/mM urine creatinine, $P=0.03$), and osteoprotegerin (OPG) (4.76 ± 0.23 vs 3.39 ± 0.17 pmol/l, $P\leq0.0001$) were increased in the HIV-infected group compared to the control subjects. Serum calcium, phosphorous, estradiol, FSH, PTH, osteocalcin and 25-hydroxyvitamin D levels were not different between the two groups, but oligomenorrhea was more common in the HIV-infected patients (38 vs 21 percent) ($P=0.03$). Among the HIV-infected women, bone density was positively correlated with lean body mass ($r=0.40$, $P<0.001$) and total body fat ($r=0.37$, $P<0.001$), and negatively correlated with urinary NTx ($r=-0.28$, $P=0.01$). Bone density did not differ by current or prior protease inhibitor (PI) or nucleoside reverse transcriptase inhibitor (NRTI) use, or differ by past or current medication status. *CONCLUSION:* HIV-infected women demonstrate reduced bone density in comparison to age- and BMI-matched female subjects of similar weight and racial composition. Increased bone resorption and altered nutritional status, hormonal function and body composition may contribute to the observed reduction in bone density in HIV-infected women. Consideration should be given to testing bone density in HIV-infected women with significant risk factors for osteopenia.

## Abstract 34: Are coronary heart disease and peripheral arterial disease associated with tobacco or cannabis consumption in HIV-infected patients on protease inhibitor antiretroviral regimens?

*G Chêne et al.*

*PURPOSE:* Tobacco and cannabis have a vasoconstrictor effect on the vascular system. Their consumption is frequent among HIV-infected patients. The investigators prospectively assessed the rate of coronary heart disease (CHD) and peripheral arterial disease (PAD) in a cohort of HIV-infected patients started on a protease inhibitor (PI)-containing antiretroviral regimen (APROCO Cohort, ANRS EP11) and the relative contribution of risk factors. *METHODS:* The APROCO Cohort enrolled 1,281 HIV-1 infected adults (77 percent male, mean age 38 years) at the initiation of a PI regimen (baseline). Serious adverse events were prospectively notified by the clinicians and validated by an Events Committee. In this analysis, only CHD and PAD were considered. Alcohol, tobacco and cannabis consumption were estimated through patients' self-questionnaires. A Poisson regression was used to analyze risk factors. *RESULTS:* By 31 March 2003, 22 patients had reported 25 events during 4,189 person-years of follow-up, ie, 5.3 per 1,000 person-years (95 percent confidence interval: 3.1 to 7.5). Events were mainly CHD (n=19), with very few lower limb arteritis (n=3) and cerebrovascular disease (n=3). A majority of patients declared smoking [43 percent ≥10 cigarettes/day (heavy smokers), 19 percent <10 cigarettes/day (light smokers)] and 21 percent admitted regular cannabis use. Incidence (per 1,000 person-years) of CHD/PAD events increased with age and smoking: 0 in patients aged 18 to 24 years, 1.9 (0 to 4.1) for 25 to 34 years, 4.9 (1.5 to 8.2) for 35 to 44 years and 13.2 (5.4 to 20.9) if >45 years ($P=0.002$); 2.0 (0 to 2.3) in non-smokers, 1.4 (0 to 4.2) in light smokers and 9.8 (4.8 to 14.8) in heavy smokers ($P=0.003$). Cannabis users had a lower, although not significant, rate [1.7 (0 to 4.9) vs 6.0 (2.9 to 9.0) in non-users]. The rate of CHD/PAD did not significantly differ according to gender, alcohol consumption, baseline CD4 cell count, HIV RNA or type of PI or nucleoside analogs prescribed. In the multivariate analysis, only age and tobacco consumption ≥10 cigarettes per day remained significantly associated with CHD/PAD morbidity. *CONCLUSION:* These data suggest that aging and smoking are important risk factors for cardiovascular morbidity but the overall rate remains low, comparable with other observational cohorts of patients treated by PI. Smoking cessation should seriously be considered in these patients and should be added to the guidelines of optimal clinical management of HIV infection.

## Abstract 35: Predictors of atherosclerosis and atherosclerotic progression in patients with HIV: the role of traditional and immunological risk factors

*P Hsue et al.*

*PURPOSE:* Preliminary evidence suggests that treated HIV-infected patients are at increased risk for coronary events. However, the relationships among cardiovascular risk factors, HIV disease and treatment and atherosclerosis have not been well defined. The purpose of this study was to identify predictors of carotid artery intima-media thickness (IMT), a marker of atherosclerosis, in HIV-infected patients at baseline and to follow IMT progression over one year. *METHODS:* The investigators measured lipids, inflammatory markers and IMT by ultrasound in a cross-sectional study of HIV-infected adults. They also assessed cardiovascular disease (CAD) risk factors, HIV disease characteristics and fat distribution. The primary endpoint was the mean maximal IMT of 12 pre-selected segments in the carotid arteries. Multivariable linear regression was used to identify independent predictors of baseline IMT and IMT progression. *RESULTS:* A total of 147 HIV-infected patients were studied; 122 patients were male. The mean age was 45 (±8) years. The mean duration of HIV infection was 11 (±4.5) years, the median nadir CD4 count was 110 cells/mm$^3$ and the median duration of protease inhibitor treatment was 3.3 years. Eighty-two patients were current smokers, 34 had hypertension and eight had CAD. The mean baseline IMT was 0.90 (±0.30) mm, which was higher than the IMT obtained from an age-matched HIV-negative control group of 63 subjects, 0.70 (±0.20, $P=0.0001$) mm. Multivariable predictors of baseline IMT were: age ($P<0.001$); low-density lipoprotein (LDL) cholesterol ($P=0.002$); cigarette pack years ($P=0.001$), Latino race ($P=0.047$), nadir CD4 ≤200 ($P=0.072$) and hypertension ($P=0.091$). When the control group was added to the analysis, HIV infection was an independent predictor of IMT ($P=0.001$). The rate of progression in 79 HIV patients was 0.10 (±0.10) mm compared to 0.01 mm in published reports of HIV-negative populations. Age ($P=0.01$), Latino race ($P=0.024$) and CD4 nadir ($P=0.049$) were multivariable predictors of IMT progression. *CONCLUSION:* Carotid IMT is higher in HIV-infected patients than in age-matched controls and progresses more rapidly than in published reports of HIV-negative cohorts. In HIV patients, carotid IMT was associated with classic coronary risk factors, and nadir CD4 ≤200. These data suggest that immunodeficiency, along with traditional cardiac risk factors, contributes to atherosclerosis in HIV-infected individuals.

## Abstract 43: Incidence of pre-diabetes and diabetes in the Multicenter AIDS Cohort Study

*TT Brown et al.*

*PURPOSE:* Abnormalities in glucose metabolism, including insulin resistance and hyperglycemia, are described with increasing frequency in patients with HIV and result from both direct and indirect effects of highly active antiretroviral therapies (HAART). While retrospective studies have estimated the risk of diabetes and insulin resistance in HAART-treated patients, the incidence of pre-diabetes and diabetes has not been well defined in a prospective cohort. *METHODS:* The investigators examined the incidence of pre-diabetes [fasting plasma glucose (FPG) ≥110 and <126 mg/dl] and diabetes (FPG ≥126 mg/dl) among 627 men enrolled in the Multicenter AIDS Cohort Study. The men included in this analysis had a baseline visit on or after April, 1999 with a FPG ≤105 mg/dl and had no history of diabetes mellitus. Of these 627 men, 288 were HIV-negative and 339 were HIV-infected (248 on HAART at baseline). Rates were calculated per 100 person-years, with 95 percent confidence intervals (CI) based on the Poisson distribution, and hazard ratios with 95 percent CI were estimated by Cox regression. *RESULTS:* Seventy-one of 627 men incurred incident pre-diabetes or diabetes (FPG ≥110 mg/dl) in 1,075 person-years, yielding an overall rate of 6.6 cases per 100 person-years (95 percent CI: 5.2, 8.3), and 28 men incurred incident diabetes in 1,110 person-years yielding an overall rate of 2.5 cases per 100 person-years (95 percent CI: 1.7, 3.7). After adjustment for age and body mass index (BMI), the hazard of pre-diabetes or diabetes among the HIV-infected HAART group was 1.4 (95 percent CI: 0.8, 2.4) times that of the HIV-negative group and the hazard of diabetes among the HIV-infected HAART group was 1.8 (95 percent CI: 0.8, 4.2) times that of the HIV-negative group. Neither estimate was appreciably altered ($P=0.32$) by partitioning the 196 HIV-infected men using protease inhibitor (PI)-containing HAART from the remaining 52 HIV-infected men using a PI-sparing HAART regimen. *CONCLUSION:* HIV-infected men, on HAART at baseline, appeared to develop pre-diabetes and diabetes at a higher rate than HIV-negative men, independent of age and BMI. Additional follow-up is needed to confirm these findings and to disentangle the particular therapy or combination of therapies contributing to this apparent increased diabetes risk.



# Peter Mugyenyi

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

This month, *IAPAC Monthly* is proud to feature Peter Mugyenyi, who is Director of the Joint Clinical Research Centre, Kampala, Uganda.

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**What proverb, colloquial expression, or quote best describes how you view the world and yourself in it?**
"The world is a stage where everyone is an actor with a role to play, but without compassion the play flops."

**What activities, avocations, or hobbies interest you? Do you have a hidden talent?**
My avocation is architectural planning and building. My hidden talent is in fine art, especially painting.

**If you could live anywhere in the world, where would it be?**
I would choose to live in Africa because there is so much to do and so little to do it with. This situation refines improvisation and sharpens imaginative thinking, providing infinite opportunities to make meaningful, practical, and much needed contribution. It is an opportunity to serve.

**Who are your mentors or real life heroes?**
My real life hero is Nelson Mandela because he stood up for what he believed in, suffered without bitterness, and emerged from it all with magnanimity, simplicity, humility, and faith in mankind.

**With what historical figure do you most identify?**
Mahatma Gandhi demonstrated that love and peace are powerful winners.

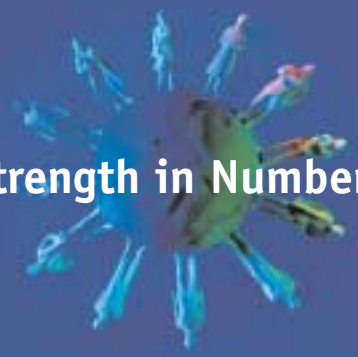
**Who are your favorite authors, painters, and/or composers?**
It is difficult to describe a single favorite author, as I like many for particular topics, subjects, or occasions. My reading ranges from old authors including William Shakespeare to modern, popular authors.

**If you could have chosen to live during any time period in human history, which would it be?**
The period after the Second World War offers greatest excitement in its scientific and social development but also posed the greatest challenges to mankind, including highly destructive weapons, disease, and environmental depreciation.

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

**In your opinion, what are the greatest achievements and failures of humanity?**
The greatest achievements of humanity so far are the scientific and technological developments as well as information and communication advances. The greatest failures remain inequity, rampant poverty, and intolerance.

**What is your prediction as to the future of our planet one full decade from present day?**
The next decade promises more of the same problems related to the pressure on [environmental] protectionism, especially in geopolitics. However, I see some ray of hope from [advances against] the scourge of HIV/AIDS, anti-tobacco campaigns, and other pro-health moves, which will help in global health awareness and possibly form a basis for a new generation of public health intervention strategies, especially in poor countries. ■



# [Strength in Numbers]

## [IAPAC Welcomes New and Renewing Members]

In September 2003, the International Association of Physicians in AIDS Care (IAPAC) welcomed 21 new and renewing dues-paying members from four 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.

William Babumba, *United Kingdom*
Tracy Betina Caldwell, *USA*
Karl Brown, *USA*
Cyndee Burton, *USA*
Linda Dean, *USA*
Jeffrey Dinsmore, *USA*
Nagib Fares, *USA*
Manfred Forstenlehner, *Austria*
Lee Francis, *USA*
Jorge Galindo-Sainz, *USA*
Lisa Hirschhorn, *USA*
Kimberly Hodges, *USA*
Phyllis Kephart, *USA*
Maurizio Bonacini, *USA*
Judy Miyakawa, *USA*
Steven Nesheim, *USA*
Mary Jo Ohara, *USA*
Paul Quinn, *USA*
Anand Sakte, *India*
Silver Sisneros, *USA*
Aimee Wilkin, *USA*

Also, the following are new and renewing institutional members: Austin Travis County MHMR Center, and Minnesota AIDS Project.

To learn more about professional and institutional memberships, call (312) 795-4935 or send an e-mail to member@iapac.org. For more 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 2003, 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.



**We prefer to negotiate but we have to change our legislation so that we can produce [these drugs] locally or import them from countries that can sell them for a lower price.**
*Alexandre Grangeiro, Head of Brazil's National AIDS Program, quoted in a September 5, 2003,* Wall Street Journal *article about his country's decision to allow imports of generic copies of patented antiretroviral drugs. The Brazilian government had been in negotiations with Abbott Laboratories, Merck & Co., and Roche Pharmaceuticals to secure at least a 40 percent discount in the prices of their patented antiretroviral drugs— lopinavir/ritonavir, efavirenz, and nelfinavir, respectively. Grangeiro said those negotiations had not advanced, thus forcing President Luiz Inácio Lula da Silva to sign a decree enabling Brazil to acquire generic antiretroviral drugs from countries such as India and China. Brazil's national AIDS program, touted as the model for antiretroviral therapy expansion, relies on the manufacture and free distribution of generic versions of antiretroviral drugs to all who need them. The country produces seven of the 14 drugs it distributes. But, according to unnamed Brazilian health officials, the cost of the three patented drugs, which the country does not produce, accounts for 63 percent of its US$200 million AIDS drug budget.*

**I didn't talk to one person who thought that. Everybody told me, "Our biggest problem is structure, manpower, and training." So not everything can be done in the first day, and many of the people we met said, "Make sure you spend the money wisely. We want every penny of that $15 billion."**
*US Senator Lamar Alexander (R-Tennessee) in a September 4, 2003, interview on Public Radio International's "The World" about ongoing appropriations debates around funding levels for US President George W. Bush's Emergency Plan for AIDS Relief. Alexander was part of a six-member congressional delegation, which also included US Senators Norm Coleman (R-Minnesota), Bill Frist (R-Tennessee), Mike DeWine (R-Ohio), Mike Enzi (R-Wyoming), and John Warner (R-Virginia), that traveled last month to Botswana, Mozambique, Namibia, and South Africa to meet with government and public health officials, physicians, and HIV-positive people. Alexander said that the US$15 billion over five years that was pledged by Bush and authorized by the US Congress for this global AIDS relief plan "will be spent, period." Yet, although US$3 billion was authorized for the first year of the plan, the Bush administration has only requested a US$2 billion appropriation for the first year. Alexander defended the Bush administration's position, stating that, "my sense of things is that the African system can't absorb too much money too quickly."*

**Why is there always so much money for war and only pennies for the human condition?**
*Stephen Lewis, United Nations Special Envoy for HIV/AIDS in Africa, in a keynote address delivered September 15, 2003, at an Honoring Our Heroes tribute dinner in Chicago hosted by the International Association of Physicians in AIDS Care (IAPAC). Lewis was honored with the 2003 Jonathan Mann Health Human Rights Award for his passionate advocacy of the HIV/AIDS cause on the African continent. Other honorees included Sister Mary Elizabeth (aegis.org), Glenda Gray and James McIntyre (South Africa), Peter Mugyenyi (Uganda), Medicus Toronto, and Pfizer Inc.*

**Some flee from place to place with the constant threat of exposure as "carriers" of the "plague."**
*Excerpted from a 94-page Human Rights Watch report released September 3, 2003, claiming that HIV is spreading unchecked in China with patients denied treatment and health officials failing to halt an unregulated blood-for-money collection scheme that has contributed to millions of HIV infections. The report is based on dozens of interviews with HIV-positive patients, AIDS advocates, HIV care providers, and police in Beijing, Hong Kong, and Yunnan province. Citing government documents, Human Rights Watch also asserts that the number of Chinese people living with HIV/AIDS is much higher than the 1 million China has admitted. Brad Adams, Executive Director of Human Rights Watch's Asia division, explained that government-sanctioned discrimination is forcing men, women, and children with HIV/AIDS to live as outcasts.*