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Five ways to tackle toxicity
(or the ant, the spider, and the bee)

FEATURE: Adverse Drug Reactions and Lipodystrophy in HIV

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Mark Mascolini

While ever more intricate theories explaining facets of HIV lipodystrophy emerge from ongoing lab work, humbler clinical studies have yielded at least five effective ways to counter antiretroviral side effects. All five enjoyed further refinement at the 6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV.

D E P A R T M E N T S

R E P O R T   F R O M   T H E   P R E S I D E N T

If only in a dream

José M. Zuniga

Often daily events manage to seep into our REM sleep and weave themselves into our dreams. Such happened to me the night after watching a CNN report about the United Nations (UN) General Assembly's commemoration of the 60th anniversary of the liberation of Nazi death camps. I was especially struck by the keynote address delivered by Elie Wiesel, one survivor of the Holocaust that killed 6 million Jews.

"The Jewish witness that I am speaks of my people's suffering as a warning," the 77-year-old told the 191-member UN General Assembly. "He sounds the alarm to prevent these tragedies from being done to others. And yes, I am convinced if the world had listened to those of us who tried to speak we may have prevented Darfur, Cambodia, Bosnia, and naturally Rwanda."

In hearing those words, I could not help but reminisce about those haunting black-and-white images depicted in documentaries about the Holocaust. Images of horror captured by the Nazis in an attempt to memorialize the inhuman acts they committed against so many men, women, and children... revealing what horrors humans can inflict upon each other in the name of some perverse ideology. Also images of hope, such as those photographs taken by American and Russian soldiers as they liberated concentration camps and found survivors... revealing a triumph of the human spirit against sheer evil.

In my dream, a similar commemoration was taking place. This time, the UN General Assembly was convened to commemorate the anniversary of eradicating HIV/AIDS. Speaking to the august body was one survivor of a plague that to date has killed

more than 30 million men, women, and children worldwide. Taking the guise of our South African colleague, Zachie Achmat (funny how our brains work), this survivor spoke of the devastation wrought by the AIDS pandemic, and sounded a warning for responses to life-threatening diseases of epic proportions.

"I was among the 'infected' once, and so I speak to you as a both a survivor and a witness of the worst plague to affect humankind in modern history. I do so as a warning to you and to future generations," the now octogenarian Achmat said in my dream. "Never again can humanity turn its back on the suffering of even the least of its brethren, never again can the affluent nations of the world abrogate their responsibility toward the poorest nations on the Earth, never again can dogma trump science, never again can profit outweigh charity, and never again can we allow so many millions of our

brothers and sisters to die as a result of our collective neglect."

I wonder if, as with the images of the dead and the "walking dead" taken at the infamous Auschwitz-Birkenau concentration camp, images of the ravages wrought by AIDS will provoke in us all feelings of regret and shame at not having done more sooner. For certainly, there are images so evocative (some published in last month's *IAPAC Monthly*) of the horror lived by millions 60 years ago—most notably of suffering and death of millions in sub-Saharan Africa. Will these images someday be joined in our memories by more hopeful ones depicting a triumph of the human spirit—aided by charity, compassion, and science—against this insidious virus?

In one of those rare instances, I can recall this dream vividly. And, as I do so, I am saddened by the reality that it is only a dream far from becoming reality. For we live in a world in which, in 2004, 4.9 million people became newly HIV-infected; in which 3.1 million people died of AIDS-related complications; in which countless millions are without access to life-saving and -enhancing antiretroviral drugs; and in which the will to improve the lot of so many men, women, and children often ebbs and wanes with the political winds. So, as we start 2005, let us recommit to overcoming the obstacles that lie in the way of achieving our dream of freeing the world of HIV/AIDS. And, as important, let us heed both Elie Wiesel's real-time and Zachie Achmat's dream-state warnings: Let us not look back 10, 20, 30 years from now and regret that we did not do more. ■

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Five ways to tackle toxicity (or the ant, the spider, and the bee)

Those who have treated of the sciences have been either empirics or dogmatical. The former like ants only heap up and use their store, the latter like spiders spin out their own webs. The bee, a mean between both, extracts matter from the flowers of the garden and the field, but works and fashions it by its own efforts.

—Francis Bacon[1]
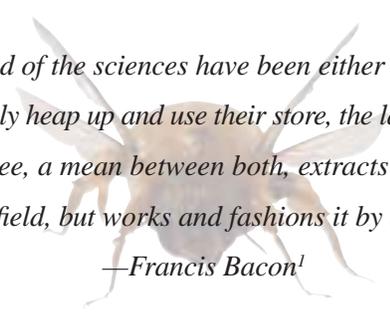
Mark Mascolini

Francis Bacon's cunning conning of scientific endeavor, quoted above, reads well five centuries later. Too much data, or too many theories, Sir Francis averred, becloud THE ADVANCEMENT OF SCIENCE. Data-driven ants and theory-spinning spiders, make way for those sedulous bees, busy blending fact and fancy to fashion hives both sturdy and productive.

In the best Baconian spirit, those bustling bees of HIV metabolics buzzed in to the 6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV with a honeycomb of hypotheses sticky with lab-gathered actualities. Attendees heard, for example, that:

- SREBP-1, heretofore implicated in protease inhibitor (PI)-induced glucose and lipid churnings, reached higher levels in livers of people with HIV lipodystrophy than in uninfected people with non-alcoholic fatty liver disease or controls without liver disease.[2] So, suggested Jacqueline Capeau (Saint-Antoine Hospital, Paris), this sterol response element binding protein may lie behind steatosis in people taking PIs. If so, these findings from Capeau's bench may mean nucleoside reverse transcriptase inhibitors (NRTIs) are not the only drugs that favor fatty livers in people with lipodystrophy.

- Luring antiretroviral-treated men with the promise of a 50 g/m^{2} "fat challenge," J.P.H. van Wijk (University Medical Center, Utrecht) found that the fat load spawned significantly higher free fatty acid and triglyceride spikes in men with lipoatrophy than in those without subcutaneous fat wasting.[3] He proposed that fat cell triglycerides don't sponge up free fatty acids as well as they should in people with lipoatrophy, leaving too many fatty acids fluxing about the body instead of settling down where they should.

- Dominic Reeds (Washington University, St. Louis) found significantly less adiponectin—and significantly worse insulin resistance—in men with Case Definition-defined lipodystrophy[4] than in HIV-infected men without this syndrome.[5] Levels of both adiponectin and interleukin 6 independently predicted glucose disposal and may contribute to insulin resistance in people with HIV.

In recent years these and other Bacon bees have bedazzled Lipodystrophy Workshop workmates with ever more expertly fashioned insights into the responses of fat, liver, bone, muscle, and immune cells to HIV, PIs, NRTIs, insulin, glucose, and lipids. Their multicelled models of the mechanisms at play sometimes rival the most encombed apiary. If their work has yet to yield the key to HIV lipodystrophy, that may be a function of time. They have labored only six years in the "Lipodystrophy Era," to judge by this workshop's numerology.

Though empty-headed theorem-threading spiders have largely quit this field, those datum-heaping ants have not. One may even judge Bacon too harsh on these down-to-earth day laborers. While the bees make honey in their skylit manufactories, the soldier ants of HIV research tunnel through adumbral realms of cohort studies, case-control comparisons, and clinical trials. To some effect. In these past six years they have unearthed five routes toward tackling toxicity. These routes provide the roadmap not only for this Lipodystrophy Workshop review, but also the reigning scheme for clinical management of antiretroviral side effects:

- Treat the toxicity with another drug
- Plan antiretroviral therapy better
- Use less toxic antiretrovirals
- Don't give up on diet and exercise
- When all else fails, call the surgeon

TREAT THE TOXICITY

Asking a person to take another drug to solve a drug-induced problem can seem an antic rather than antlike solution, even when the person in question would *rather* take another drug than do something awful like diet. Everyone appreciates the
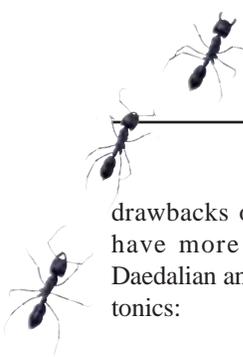
drawbacks of this approach, which can have more dead ends than the most Daedalian anthill. To name a few, antitoxic tonics:

- Don't always work
- Can cost a lot
- Come with their own problems
- Can foul up antiretroviral action
- Can complicate adherence

Yet the alternatives to pouring new anodynes on "adverse events" often prove scarce or risky (like switching from a working regimen), so HIV docs find themselves writing more and more scrips for drugs that trim triglycerides, cut cholesterol, or knock some sense back into insulin-insensitive islet cells. Lena Normén (University of British Columbia, Vancouver) surveyed the scope of that scale-up in a study of 237 HIV-infected people seen at the HIV Metabolic Clinic of St. Paul's Hospital from 1999 through 2003 [abstract 76]. In choosing that population she chose people with a high likelihood of unwanted antiretroviral activities.

Men far outnumbered women in this study group (94.5 percent), and PI regimens proved the prime therapy in 86 percent. But the PI takers didn't differ from their non-PI confreres in number of other drugs taken or the cost of those drugs. (The report did not clarify how many people in the non-PI group had once tried a protease drug.) Use of lipid-limiting statins and fibrates and insulin-sensitizing medicines all rose from study entry through six months of follow-up (Table 1). Antitoxicity drug costs also climbed in those six months.

The more-than-doubled use of these drugs in this half year should inspire no surprise: These people had lipid and glucose problems bad enough to require referral to a specialized clinic where pharmacotherapy must figure prominently. (In a California population of 15,000 people taking PIs, reliance on lipid lowerers jumped 6-fold from 1.7 percent in January 1996 to 10.6 percent in June 2002.[6]) The scandent drug costs in British Columbia may not be a problem for people living there or for others with blanket healthcare coverage; they would be elsewhere.

Table 1. **Rising use and cost of drugs for side effects**

	Statins	Fibrates	Insulin sensitizers
Baseline use (%)	19	17	11
Use at six months (%)	39	46	27
Baseline cost* (US$)	$12.95	$10.22	$8.32
Cost at six months* (US$)	$13.63	$14.91	$9.15

*Average monthly cost per person in British Columbia.
Source: Lena Normén, abstract 76.

A safer way to exploit growth hormone?

No drug typifies the promise and perils of antitoxicity therapeutics better than recombinant human growth hormone (rhGH). Though it surely sculpts unwanted visceral fat from people with HIV lipodystrophy, rhGH has problems. It can leave the skin painfully taut and turgid, it poses risks for people prone to diabetes, it costs a lot, and when people stop taking it the fat comes back.

Ever since the 2nd Lipodystrophy Workshop in 2000,[7] researchers who grasp the merits of rhGH have groped for a tolerable maintenance dose that will keep fat off while keeping costs down. Either 1 or 2 mg daily may get the job done without stirring up insulin resistance.[8] But a six-month study of 1 mg in five men charted visceral fat drops only in those who started the study with the most visceral fat, while finding no improvement in waist width or waist-to-hip ratio.[9]

Does rhGH work in HIV-infected adolescents with too much visceral fat? Sometimes yes, sometimes no, according to a 24-week pilot study by Alessandra Viganò (University of Milan) [abstract 1]. She gave rhGH in a dose of 0.026 mg/kg daily to five girls and three boys with more than 42 cm^2 of visceral fat at the L4 slice of an MRI scan. They ranged in age from 13.7 to 18.5 years and had a median CD4 count of 706 cells/mm^3 after a median 79.5 weeks of antiretroviral adventures.

Visceral fat fell significantly ($p = 0.01$) by an average 40 percent (range 19 to 70 percent) during the 24 weeks of treatment. Compared with 97 children matched for age and weight, the treated children lost significantly more total fat, trunk fat, arm fat, and leg fat. Total, trunk, arm, and leg lean mass climbed significantly more in the kids taking rhGH than in the control

group. Viganò said the gains in arm and leg lean mass offset the loss in subcutaneous fat; the kids' arms and legs ended up looking better, she contended. Fasting glucose, triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol did not change significantly.

At the 24-week point, four children had less than 41 cm^2 of visceral fat—the treatment goal—and four children did not. The children who reached that goal switched to a lower maintenance dose of rhGH, while the other children continued the starting dose.

Another study at the Lipodystrophy Workshop in 2000 staked out a rationale for giving growth hormone to HIV-infected people with too much fat of the visceral variety: Men with high visceral fat sums had low natural levels of growth hormone.[10] But injecting rhGH isn't the only way to replete skimpy growth hormone stores. One might also try giving growth-hormone releasing factor (GRF), available as an investigational product labeled TH9507. Or one might try growth hormone-releasing hormone (GHRH). Steven Grinspoon (Massachusetts General Hospital, Boston) has tried both.

A 12-week placebo-controlled trial of GHRH published a few months before the Workshop tallied significant improvements in body mass, trunk fat, ratio of trunk to leg fat, and ratio of abdominal visceral fat to abdominal subcutaneous fat in 31 HIV-infected men with lipodystrophy.[11] GHRH had no significant impact on glucose, insulin, or lipids during this brief trial.

At the 2004 Lipodystrophy Workshop, Grinspoon served up results of a 12-week placebo-controlled look at 1 or 2 mg of GRF daily in HIV-infected people with a waist-to-hip ratio above 0.93 in the 54

men and above 0.87 in the seven women [abstract 2]. All study participants had taken a stable antiretroviral combo for at least eight weeks.

Levels of IGF-1 (the endocrinologist's barometer of growth hormone drug activity) jumped 59 percent in the 17 people randomized to 1 mg of GRF ($p = 0.002$) and 88 percent in the 15 people randomized to 2 mg ($p < 0.0001$). Those numbers establish a dose response to this agent.

Compared with the placebo and 1-mg groups, people taking 2 mg of GRF enjoyed significant ebbs in total fat and trunk fat ($p = 0.01$ for both comparisons). Total and trunk fat both fell about 2 kg in people taking the 2-mg dose. CT-measured visceral adipose tissue waned 21.5 cm^2, a 16 percent dip, in people taking 2 mg of GRF ($p < 0.05$ versus baseline). The visceral-to-subcutaneous adipose tissue ratio improved significantly in both GRF groups compared with the placebo group ($p < 0.05$).

HDL cholesterol rose slightly and triglycerides dropped in people assigned to 2 mg of GRF. Fasting insulin (but not fasting glucose) also climbed some in that group, and 11 of 21 people taking 2 mg complained of headache or burning or prickling sensations. Three people quit the 2-mg group because of side effects—rash, prickling, and joint pain.

Researchers have a phase 3 study of GRF on the drawing boards. Both GRF and GHRH merit close attention to see if they work as well as rhGH with fewer side effects. Visceral fat didn't drop as much with GRF as it has in rhGH trials, but people in the rhGH studies had higher starting fat loads. Grinspoon observed that the adipose tissue drop with GRF matches that with rhGH when reckoned as change in order of magnitude.

Will uridine have a role?

Since the 4th Lipodystrophy Workshop two years ago, Ulrich Walker (Medizinische Universitätsklinik, Freiburg, Germany) has been tantalizing toxicity mavens with *in vitro* visions of a drug that may undo NRTI damage to mitochondria. Although placebo-controlled studies of uridine have started in people with HIV, Walker unveiled only new lab dish data at this Lipodystrophy Workshop. Having proved

uridine's prowess in liver cells last year,[12] this time he looked at the drug's doings in adipocytes [abstract 14].

Walker doused fat cells with 10 µM of stavudine (d4T) or 0.2 µM of zalcitabine (ddC) for 21 days with or without 200 µM of uridine. In cells exposed only to NRTIs, d4T or ddC stymied lipid accumulation (by 36 percent and 20 percent) and swelled cell suicide rates (5.6-fold and 2.2-fold). The damage seemed driven by mitochondria, since d4T depleted mitochondrial DNA (mtDNA) stocks by 64 percent ($p = 0.006$) and ddC by 55 percent ($p = 0.01$).

Uridine changed all that. Fat cells incubated with d4T and 200 µM of uridine had the same cell death rate as untreated adipocytes. Lipid content in both d4T- and

ddC-treated cells stood at near-normal levels when also bathed in uridine. And uridine reversed mtDNA downturns in both d4T- and ddC-treated adipocytes. Because uridine fixed everything d4T or ddC broke, Walker proposed that these drugs' toxic insults can be traced to cellular depletion of uridine or its metabolites.

Europeans with addled adipocytes can pick up uridine at their local health food store, sold as mitocnol under the brand name NucleomaxX. Walker tested mitocnol in healthy volunteers, who downed 36 g of the stuff dissolved in a glass of orange juice [abstract 30]. Because these four men and four women averaged maximum concentrations of 152 µM, Stefan Mauss (Center for HIV and Hepatogastroenterology, Düsseldorf) worried that the 200 µM used

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What is this thing called "lipodystrophy"?

The Lipodystrophy Workshop started back in the last century with a mission to define the syndrome in people with HIV. Breakout session stalwarts at that first workshop grappled with the meaning of fat wasting, fat accumulation, lipid and glucose disturbances, and "other manifestations," then reassembled for a hopefully titled parliament on "Reaching a consensus—lipodystrophy case definition."

But consensus proved as elusive as fat in atrophic forearms and the workshop's focus soon shifted to the hard science of HIV metabolics. A team spearheaded by Andrew Carr (St. Vincent's Hospital, Sydney) did go on to forge a case definition that reignited the glossologic debate. Most attendees at that first workshop would have concurred with the large and small print of the Case Definition,[4] until the FRAM study posed prickly questions about where central fat buildups fit into the syndrome.[13] The problem, all will recall, is that FRAM's non-HIV control group did so well in stacking on central pounds that magnified midriffs failed to distinguish the lipodystrophic from the average guy without HIV.

That problem is not wholly American, observed Enzo Bonora (University of Verona) at the 6th Lipodystrophy Workshop [abstract P6]. His review of the Bruneck study—Italy's answer to the Framingham Heart Study—noted that 70 percent of people in that cohort have too much fat under the cumberbund.

With anguished polemics over lipohypertrophy on the wane, Carr took a calm look at how the Case Definition fared in framing lipodystrophy among people enrolled in the 96-week trial comparing tenofovir (TDF) with stavudine (d4T) in treatment-naive people also starting lamivudine (3TC) and efavirenz (EFV)[14] [abstract 11]. The definition uncovered more than twice as many lipodystrophy cases than did unprompted side effect reports tendered by trial clinicians.

Carr based his comparison on a Case Definition model that included DEXA fat scans (done at week 96 in the study) but excluded CT scans and waist-to-hip ratio (which were not collected in the TDF trial). In this subset of 255 trial participants—fewer than half of the 600 enrollees—17 (7 percent) had lipodystrophy at week 96 according to physician reports. But the Case Definition saw lipodystrophy in 48 people (19 percent) after 96 weeks, 40 (31 percent) taking d4T and eight (6 percent) taking TDF. Only seven of those 48 (15 percent) had lipodystrophy according to trial physicians' report cards.

A multivariate analysis picked out four factors that independently raised the risk of lipodystrophy:

- d4T versus TDF: odds ratio 8.7, $p < 0.001$
- Older age: odds ratio 1.08 per year, $p = 0.001$
- Female versus male: odds ratio 3.7, $p = 0.001$
- Higher pretreatment triglycerides: odds ratio 1.32 per mmol/L, $p = 0.021$

The greater sensitivity of the Case Definition could improve diagnostic accuracy in clinical trials, Carr argued, while yielding a uniform body of data. But Michael Dubé (Indiana University, Indianapolis) offered a contrary hypothesis: Carr's findings may say the Case Definition is too sensitive and hence less accurate.

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in Walker's fat cell studies sits on the high end of the concentration range in humans (116 to 210 µM in Walker's study).

Another practical question is who might use uridine supplements. Walker thinks uridine stifles mtDNA depletion by helping cells tank up on lost pyrimidine. Because didanosine (ddI) is a purine analog, he does not expect that uridine will curb its mitochondrial depredations. (It didn't in the liver cell study.[12]) And with d4T following ddC into the Museum of Unused Nucleosides, uridine may end up with fewer problems to solve. It did help reverse zidovudine (AZT)-induced damage in the liver cell study, but Walker didn't test AZT in the fat cell experiments.

Are statins worth the risk?

Statins can cut high cholesterol, but these drugs are no elixir for lipid-laden people with or without HIV. The statin that interferes least with PIs—pravastatin—finished second to atorvastatin (40 versus 80 mg daily) in a ballyhooed clinical endpoint trial involving people without an HIV diagnosis.[15] Three Lipodystrophy Workshop studies found that statins either fall short in lowering antiretroviral-hoisted lipids or have little effect on other markers despite trimming cholesterol. On top of that, workshop attendees learned, statins may blunt CD4 gains and further muck up mitochondria in already-aggrieved cells. A newer cholesterol cleaver that doesn't bollix PI-metabolizing enzymes, ezetimibe, got a look in HIV-infected people already taking other lipid lowerers.

Treatment with a statin or gemfibrozil helped few people reach US National Cholesterol Education Program (NCEP) lipid goals in a retrospective analysis of 53 antiretroviral-treated men presented just after the workshop.[16] Everyone had a cholesterol or triglyceride reading above 200 mg/dL while taking antiretrovirals and tried an antilipid drug for more than two months. Twenty-seven of these 53 men had cardiovascular disease or the coronary artery disease risk equivalent at the beginning of follow-up. Twenty had dietary changes or nutritional counseling.

Half of these men took pravastatin at a mean dose of 16.7 mg, while 12 took simvastatin (presumably not with PIs,

which dangerously boost simvastatin levels). Seven took gemfibrozil and one atorvastatin. Fourteen men were taking two PIs and 37 at least one PI.

Average total cholesterol dropped from 275 mg/dL at the start of follow-up to 228 mg/dL after six months, and 30 percent of the men reached the NCEP goal of less than 200 mg/dL. Average triglycerides fell from 516 mg/dL to 344 mg/dL, and 23 percent of the men reached the sub-200 mg/dL goal. Seven men (13 percent) had a new heart disease diagnosis after starting antilipid agents. These results confirm US AIDS Clinical Trials Group (ACTG) findings that pravastatin with or without fenofibrate rarely helps antiretroviral-taking people hit NCEP targets.[17]

Even when statins do rein in unruly lipids, two Lipodystrophy Workshop studies found, they have no impact on endothelial function (a measure of blood vessel health) or carotid intima media thickness (a much-used predictor of heart disease). But a third study found that statins may keep carotid intima media thinner.

Peter Sklar (Drexel University, Philadelphia) tested pravastatin's effect on endothelial function in a placebo-controlled, double-blind crossover study involving 23 people taking a steady antiretroviral regimen [abstract 24]. He measured flow-mediated vasodilation (FMD) of the brachial artery to gauge endothelial function before randomizing people to 40 mg of pravastatin daily or placebo. Sklar refigured FMD six weeks after the pravastatin course, then six weeks after the crossover.

The baseline measure showed significantly lower FMD in these HIV-infected people than in uninfected controls enrolled in other trials (7.0 percent versus 10.1 percent, $p = 0.002$). Baseline values in the HIV group didn't correlate with viral load, CD4 count, or PI- versus non-PI therapy. Pravastatin significantly lowered total cholesterol, LDL cholesterol, and triglycerides when compared with placebo. Despite these gains, Sklar found "no consistent or significant improvement" in endothelial function after six weeks of pravastatin (7.0 percent with pravastatin and 7.3 percent with placebo).

Nor did pravastatin lower levels of C-reactive protein (CRP), a portent of heart

disease in many a trial. But the import of that finding is tough to figure since, as Sklar reported in a 180-person case-control study, CRP looks like a crabbed predictor of cardiocorrosion in people with HIV (but see note 18).

A year or more of pravastatin seemed not to protect against carotid intima media thickening in a case-control study of French people with HIV, but Canadian researchers reached the opposite conclusion in a prospective cohort study of people taking any statin. The French inquest, reported by Franck Boccara (Sainte-Antoine Hospital, Paris), compared 27 antiretroviral-treated people with an LDL above 160 mg/dL and 27 antiretroviral-treated people without bad lipids but matched to the high-LDL cases for age, gender, and tobacco use [abstract 114]. The people with high LDL averaged 1.8 years of pravastatin therapy, but otherwise they matched the controls in clinical traits and cardio risk factors other than lipids.

Carotid intima media thickness measured 692 ± 129 µm in the pravastatin group and 716 ± 46 µm in the controls, a nonsignificant difference ($p = 0.52$). Logistic regression analysis linked only age and carotid pulse pressure to intima media thickness in these people.

The longitudinal Canadian study, on the other hand, tied statin therapy to a lower risk of carotid intima media thickening through one year of follow-up [abstract 122]. Marek Smieja (McMaster University, Hamilton, Ontario) and colleagues at four other sites have signed up 300 HIV-infected people for this ongoing study. Among 162 people analyzed so far for baseline measures, intima media thickness averaged 0.82 ± 0.25 mm. A passel of variables independently predicted thicker carotid walls—age, gender, smoking, systolic blood pressure, total cholesterol, and glucose. The antiretroviral being taken had no apparent impact on intima media girth.

After one year of follow-up on 59 people, carotid intima media thickened an average 0.043 ± 0.089 mm per year, a significant clip ($p < 0.001$) confirming US findings.[19] Baseline intima media thickness and age predicted faster progression, whereas treatment with statins (but not fibrates) proved protective (Beta = -0.07, $p = 0.04$).

While wondering whether statins hasten or halt carotid caking, clinicians might also worry about whether these cholesterol clippers abet NRTI-induced mitochondrial toxicity. That news came from Michel de Baar (Primagen, Amsterdam), who unleashed simvastatin and lovastatin in peripheral blood mononuclear cells (PBMCs) and liver cells to study their effects on mtDNA and mtRNA [abstract 37].

With colleagues at Amsterdam's Academic Medical Center, de Baar reasoned that statins' especial activity—blocking HMG-CoA reductase—does more than cut cholesterol. It also lowers quotients of coenzyme Q10 (ubiquitone). And what does coenzyme Q10 do? It totes electrons in the oxidative phosphorylation (OXPHOS) system—the cell's perpetual motion machine. In other words messing with OXPHOS can mess up mitochondrial function. Doctors who prescribe statins already know they pose a long-term or high-dose mitochondrial threat manifested as muscle weakness or myopathy.

Putting these pieces together, de Baar hypothesized that cells compensate for statin-triggered loss of mitochondrial function by upping transcription and translation of enzymes critical to OXPHOS. If true, that would mean higher levels of mtDNA and mtRNA in statin-steeped cells.

The Amsterdam team gave 40 mg of simvastatin daily for two months to seven people with an LDL cholesterol above 4 mmol/L (155 mg/dL) and 100 mg of ciprofibrate daily for two months to five people with triglycerides above 4.5 mmol/L (400 mg/dL). Comparing pretreatment and two-month mtDNA and mtRNA levels in PBMCs, de Baar found significantly higher two-month totals in the statin group but not in the fibrate group.

Next de Baar doused HepG2 liver cells with 10 μM of simvastatin or lovastatin for 10 days. Compared with unexposed control cells, those drizzled with lovastatin had significant jumps in mtDNA and mtRNA, while simvastatin-treated cells had significant gains only in mtDNA.

These findings led the Amsterdam researchers to propose that statin-exposed cells make up for inhibition of coenzyme-Q10 by making more mtDNA and mtRNA. But giving a statin and a mitotoxic nucle-

Table 2. CD4 changes with or without statins

	Statin-taking cases (n = 136)	Statin-naive controls (n = 136)	p
Mean absolute CD4 change, cells/mm^3 (SD)	24 (133)	68 (187)	<0.0001
Median absolute CD4 change, cells/mm^3 (IQR)	16 (-45 to 101)	41 (-28 to 128)	0.07
Mean percent CD4 change (SD)	12 (36)	32 (95)	<0.0001
Median percent CD4 change (IQR)	3 (-12 to 30)	10 (-8 to 46)	0.08
Percent gaining at least 50 cells/mm^3	36	47	0.07

IQR = interquartile range; SD = standard deviation.

Source: Uchenna Iloeje, abstract 69.

oside at the same time could overwhelm the compensatory mechanism. With both drugs now disrupting mitochondrial function, the toxicity could be greater than with nucleosides alone. Indeed, in a T-cell line de Baar found that 1 μM of ddI had little effect on mtDNA content, 1 μM of simvastatin quintupled mtDNA content, while ddI plus simvastatin halved mtDNA content.

These hypotheses may remain too hypothetical for some, but they certainly suggest careful monitoring of statin therapy in NRTI takers already enduring mitochondrial toxicities. Perhaps a more palpable statin threat came to light in two recent studies—a blunted CD4 gain in people taking these antilipid agents.[20,21] One of these studies,[21] however, charted a return to steady CD4 gains after a year of statin therapy.

Bristol-Myers Squibb and US Centers for Disease Control and Prevention (CDC) researchers took up the scent in a case-control study comparing 136 people taking antiretrovirals and statins and 136 antiretroviral-treated people not taking statins and matched for age, gender, baseline CD4 count, and calendar year of starting antiretrovirals [abstract 69]. The groups matched well in baseline CD4s (mean 440.5 cells/mm^3 in cases and 433.6 cells/mm^3 in controls), though the statin-taking "cases" had a significantly lower mean baseline viral load (4.7 versus 5.8 logs, $p < 0.0001$) and a significantly shorter mean duration of HIV infection (9.2 versus 11.2 years, $p = 0.0002$). Most "cases" were taking atorvastatin (73 percent) or pravastatin (19 percent).

Tracking CD4 changes through the duration of statin therapy (or an equivalent span of antiretroviral therapy in the controls), Bristol-Myers Squibb's Uchenna Iloeje found significantly blunted T-cell gains in

the statin group when figured as mean changes, and marginally blunted gains when figured as median changes (Table 2). The researchers did not say how long the "cases" took statins, but by definition the shortest course was six months.

A multivariate model adjusting for baseline viral load, nadir CD4 count, and duration of HIV infection linked only statins to feebler CD4 spurts. In a model that also factored in the type of antiretroviral therapy, the statin link with lower CD4 gains inched beyond the ambit of statistical significance ($p = 0.06$). These findings beg the question whether slower CD4 crescendos mean much clinically to people starting follow-up with an average 440 cells/mm^3.

A different way to downsize cholesterol

The search for an effective, antiretroviral-friendly antilipid drug found a candidate in ezetimibe, an agent that blocks cholesterol absorption in the small intestine and neither inhibits nor induces the cytochrome P450 (CYP) enzymes that rule PI metabolism. Daniel Lee (University of California, San Diego) scoured 14 charts at the Owen Clinic to see how people fared when adding ezetimibe (10 mg daily) to ongoing lipid-lowering therapy [abstract 83]. Of the 14 men analyzed, nine were taking a PI, three a nonnucleoside reverse transcriptase inhibitor (NNRTI), and two both a PI and an NNRTI. Seven attacked high lipids with atorvastatin, three with pravastatin, two with atorvastatin plus fenofibrate, and one each with fenofibrate or niacin.

Mean non-HDL cholesterol slid from 257.4 mg/dL before antilipid therapy to 224.3 mg/dL when these men started ezetimibe (a median of 927 days into lipid-lowering treatment). Adding ezetimibe further pushed mean non-HDL cholesterol

down to 167.4 mg/dL (in a median of 336 days). The total cholesterol drop was statistically significant ($p < 0.00001$), as were the drops with antilipid drugs before ezetimibe and from the start of ezetimibe to the end of follow-up. Non-HDL cholesterol ebbed an average 35 percent throughout the whole antilipid course and 25.4 percent during treatment with ezetimibe plus the other drugs.

Rosiglitazone: Still not easing atrophy

The insulin sensitizer rosiglitazone does its job in HIV-infected people with insulin resistance, but hopes that it would also refill the hollows of lipoatrophy took a decisive blow in the 48-week double-blind, placebo-controlled ROSEY study.[22] Those still hoping that just a few more months of treatment would make a difference must now contend with the ROSEY team's 84-week results: It still didn't work [abstract 78].

When the randomized trial phase ended, participants had the option of continuing rosiglitazone or starting the drug if they'd been taking placebo. Most did. But when Andrew Carr (St. Vincent's Hospital, Sydney) and colleagues parsed the 48-week blinded results and saw no fat advantage with rosiglitazone, they stopped enrollment in the open-label follow-up.

Analyzing limb fat changes at week 84, ROSEY researchers found only a 0.02-kg difference between the glitazone and placebo groups. Both groups gained about 0.4 kg of limb fat, perhaps because many had stopped d4T or AZT. Nor did Carr discern any between-group differences in subcutaneous mid-thigh fat, subcutaneous abdominal fat, visceral fat, total body fat mass, total trunk fat, lean body mass, lipodystrophy Case Definition score, total cholesterol, triglycerides, glucose, or insulin.

Rosiglitazone did have side effects: more grade 3 or 4 triglyceride gains (in 56 percent starting with rosiglitazone versus 49 percent starting with placebo), cholesterol (26 versus 18 percent), creatinine kinase (42 versus 20 percent), and amylase (9 versus 4 percent). Carr and coworkers advised that "avoidance of drugs associated with lipoatrophy is necessary to prevent this complication."

PLAN ANTIRETROVIRAL Rx BETTER

As the just-reviewed research makes clear, antitoxicity therapeutics can be a hit-or-miss venture. Sometimes the drugs perform as advertised; sometimes they don't; and sometimes they leave other toxic litter. Wouldn't it be easier to avoid antiretroviral side effects in the first place through more prudent prescribing?

With new antiretroviral strategies and drugs to exploit, that may be possible. And as countless antiretroviral switch studies show, some side effects may even be banished, or at least slowly eased. But better treatment planning remains a work in progress, as some workshop results attest.

Can STIs make AEs go away?

Some antiretroviral side effects may prove utterly resistant to simple antiretroviral swaps. Visceral fat buildups, for example, defied switches from PIs to non-PI therapies. But out-of-line lipids, insensate insulin, and even limb fat wasting have improved after judicious antiretroviral juggling.

If stopping the offending drug helps, will stopping *all* of them help even more? That's the question asked in several structured treatment interruption (STI) studies that sought mainly to give people a drug holiday and make adverse events (AEs, the polite term for toxicity) less irksome. The record so far has been blotchy. Four recent STI studies[23-26] saw no improvement in lipids, liver enzymes, or even quality of life,[26] while one study did log lipid drops.[27]

The latest study of this ilk comes from an ACTG team topped by Pablo Tebas (Washington University, St. Louis) [abstract 20]. He and ACTG 5102 colleagues randomized 47 people with well-controlled HIV and more than 500 CD4 cells/mm^3 to pump up their T cells farther with 18 weeks of interleukin 2 (IL-2) or to sit tight for 18 weeks. Then everyone stopped antiretroviral therapy and stayed off treatment until their count dropped to 350 cells/mm^3.

A year of follow-up showed that IL-2 did not help people suspend treatment longer.[28] But lipids did drop dramatically

shortly after study participants quit therapy. The only problem was that—along with total cholesterol, LDL cholesterol, and triglycerides—"good" HDL cholesterol also plunged significantly from the baseline measure. Neither fasting glucose nor HOMA-gauged insulin resistance changed during the treatment break.

Does the drop in salubrious HDL cholesterol wipe out the benefit of the other lipid skids? A study like this can't say.

An even easier maintenance regimen?

When PI side effects started making headlines, clinicians were quick to try simpler maintenance regimens—often a nonnucleoside and two nukes. Now French researchers are trying something simpler still—a nonnucleoside and one nuke, efavirenz (EFV) and TDF [abstract 82]. So far it seems the two-drug combo is working, although there is a conventional comparison arm—3TC/TDF/EFV—and results remain blinded. But in its first two meetings the Data Safety and Monitoring Board saw no reason to stop the COOL Trial. For the whole study group, CD4 counts have been going up, and triglycerides down.

Patrick Mercié (Saint-André Hospital, Bordeaux) and coworkers recruited 140 people with fewer than 50 copies/mL for at least six months, no treatment failures on their charts, and any CD4 count. The COOL protocol excluded anyone with "significant laboratory or clinical abnormalities" or a creatinine clearance below 60 mL/min. Half of the enrollees got randomized to TDF/EFV and half to 3TC/TDF/EFV. The starting CD4 count stood at a median 475 cells/mm^3 (range 78 to 1,775 cells/mm^3). More people were taking a PI plus NRTIs (47 percent) than were taking a nonnucleoside with NRTIs (43 percent).

Among 60 people who have reached trial week 36, the median CD4 count has climbed 23 cells/mm^3. In that time the group's median triglyceride value dropped significantly from 1.4 to 0.9 mmol/L (124 to 79 mg/dL) ($p = 0.003$). (The normal range is 0.11 to 2.15 mmol/L or 10 to 190 mg/dL.) Median cholesterol and LDL cholesterol values also drifted downward through 36 weeks of treatment, but not significantly. Median HDL cholesterol stayed flat.

Four people have stopped their new regimen, two because of treatment-related side effects (dizziness and "digestive intolerance"), one because of treatment-induced hepatitis, and one because of pneumonia.

The COOL plan calls for CT scans at baseline and week 48 (and DEXA scans in a subset) to gauge fat changes.

Lofty saquinavir levels cause problems

Therapeutic drug monitoring (TDM) is one way to make sure drug levels are high enough to stifle HIV, but not high enough to trigger toxicity. Overly high levels plagued some people taking saquinavir/ritonavir (SQV/RTV) in the two MaxCmin trials, reported Jens Lundgren (Hvidovre University Hospital, Copenhagen) [abstract 79]. His poststudy scrutiny of drug levels showed that some people reached SQV levels "that far exceed those required to inhibit wild-type HIV" (0.1 μg/mL).

The MaxCmin trials both explored a twice-daily SQV/RTV dose of 1,000/100 mg. Looking at week four SQV troughs, Lundgren found that they correlated with week 48 troughs. Splitting the study group into trough-based quartiles, he counted a significantly higher proportion of grade 3 or 4 side effects in the highest quartile (34 percent) than in the lowest (12 percent) ($p < 0.05$). Bigger cholesterol jumps at week four also correlated with week four SQV quartiles ($p = 0.06$). This analysis did not tie RTV levels to cholesterol.

Lundgren proposed that SQV doses "could be reduced without loss of efficacy" in people without resistant virus.

Clues to anticipating mitochondrial toxicity

In an enlightening review lecture, Courtney Fletcher (University of Colorado, Denver) argued that clinicians can anticipate who may have a bigger risk of mitochondrial toxicity [abstract P4]. NRTI-induced mitochondrial toxicity, he explained, rests on four principles:

- The primary role of mitochondria is to power cells by fueling them with adenosine triphosphate (ATP).
- Replication of mitochondrial DNA (mtDNA) depends on DNA polymerase gamma.

- Inhibiting DNA polymerase gamma drains mtDNA tanks and causes mitochondrial dysfunction.
- NRTIs inhibit DNA polymerase gamma.

Clinical trial evidence supports this framework. For example, mtDNA and mtRNA levels rebounded smartly in blood cells and subcutaneous tissue of people who traded a nucleoside regimen for one with no NRTIs.[29] Plenty of other studies show that stopping particular NRTIs can reverse purported mitochondrial toxicities, from anemia to fat atrophy.

An array of evidence also indicates that higher levels of nucleoside triphosphates—the active NRTI form inside cells—mean more frequent mitotoxicity. And Fletcher marshaled a phalanx of data showing bigger triphosphate freightloads in two groups of people with HIV—those with more advanced disease, and women.

Fletcher's own study of people starting an AZT/3TC regimen found AZT triphosphate readings twice as high in people beginning therapy with fewer than 100 CD4 cells/mm^3 (154 fmol/million cells) than in those starting with a higher CD4 count (67 fmol/million cells), even though they started with the same dose of AZT.[30] Another study traced the same link between AZT triphosphates and pretreatment CD4 counts under 100 cells/mm^3 in people starting dual nucleoside therapy.[31] AZT monophosphate levels proved significantly higher in Thai people with HIV than in healthy volunteers.[32]

Another study by Fletcher's group recorded AZT- and 3TC-triphosphate levels twice as high in women as in men, even after statistical correction for weight.[33] This study also found that women get their viral load under 50 copies/mL faster than men, and that AZT triphosphate predicts the time to a sub-50 load while 3TC triphosphate predicts the durability of response. Once again triphosphate loads were larger in people with lower CD4 counts. Another AZT study found significantly deeper triphosphate pools in women.[34] And a comparison of four men and one woman taking abacavir (ABC) found much higher levels of carbovir triphosphate (ABC's muscled-up format) in the woman.[35]

Nucleoside doses can be adjusted, Fletcher noted, though measuring NRTI triphosphates inside cells isn't as easy as measuring PI or NNRTI levels in blood. And he allowed that factors other than triphosphates—like HIV and inflammatory cytokines—can disrupt mitochondria. But these studies suggest plenty of room for fine tuning when treating people with nucleosides.

USE LESS TOXIC DRUGS

All antiretrovirals—and all drugs, as anti-inflammatory fanciers lately learned—have their side effects. But antiretroviral research has made two important strides in this area, culling drugs with particularly toxic profiles, and devising new agents that do less harm. The workshop featured reports on mitochondrial toxicity of the thymidine analogs d4T and AZT and the relative safety of TDF. Attendees also got a look at new data on the impact of low-dose RTV, along with favorable news on atazanavir (ATV) and fosamprenavir (FPV).

AZT, d4T, TDF, and mtDNA

Ongoing work by David Nolan (Royal Perth Hospital, Australia) bolsters the mitochondrial hypothesis, which holds that NRTI-induced depletion of mitochondrial DNA (mtDNA)—particularly in fat cells—explains treatment-related lipoatrophy. Reviewing real-time PCR probes of mtDNA in fat cells sampled from 41 people not taking antiretrovirals and from 92 taking NRTI regimens, Nolan counted significantly fewer mtDNA copies in people taking d4T or AZT than in the untreated group, but no difference between untreated controls and those taking only nonthymidine analogs [abstract 16] (Table 3).

Treatment-naive people starting a regimen including d4T or AZT shed an average 263 mtDNA copies/cell monthly over the first year of therapy ($p = 0.005$). But previously untreated people launching a nonthymidine analog combo averaged only a 69-copy/cell monthly drop in mtDNA over the first year, a nonsignificant change ($p = 0.6$). Swapping d4T or AZT for ABC swelled mtDNA content in fat cells 3- to 11-fold ($p = 0.01$) in a median of six months.

Table 3. **Fat cell mtDNA content according to NRTI regimen**				
Treatment	*n*	*Log mtDNA copies/cell ± SD*	*% mtDNA vs naive*	*p*
None (HIV negative)	7	3.2 ± 1586	—	—
None (ART naive)	34	3.19 ± 1564	—	—
None (off therapy)	7	3.18 ± 1523	—	—
AZT	42	2.89 ± 771	49	<0.0001 vs naive
d4T	35	2.44 ± 275	18	<0.0001 vs naive
				<0.0001 vs AZT
ABC + 3TC or TDF	17	3.23 ± 1707	—	Not significant vs naive
3TC, TDF, and/or ddl (no ABC)	6	3.04 ± 1095	—	Not significant vs naive

Source: David Nolan, abstract 16.

An analysis adjusted for NRTI use did not link current PI therapy or age with mtDNA readings.

These findings reflect clinical evidence of slowly repleting peripheral fat in people who drop d4T or AZT in favor of ABC.[36-40] At the Workshop Sharon Walmsley (Toronto Hospital) reported little fat atrophy through 120 weeks of treatment with FPV plus—in 82 percent of study participants—3TC and ABC [abstract 50, see "Lipid and fat changes" below]. But mtDNA decimation may not be the only physiologic foible behind fat atrophy, according to results of a study by Patrick Mallon (University of New South Wales, Sydney) [abstract 15]. Sizing up mitochondrial and nuclear gene expression in 20 healthy volunteers who took d4T/3TC or AZT/3TC for six weeks, Mallon saw stunted mitochondrial RNA transcription with no significant mtDNA depletion.

If switching from d4T to ABC rebuilds leg and arm fat, what about switching to TDF? That tradeoff also pays peripheral fat dividends, results of a 10-person study suggest [abstract 47]. George Tsekes (Hellenic Red Cross Hospital, Athens) rated regional and total body fat changes with DEXA scans before these people switched to TDF and 52 weeks later. All had physician-diagnosed lipodystrophy before starting TDF, and none switched other drugs in their regimen.

CD4 counts stayed stable through 52 weeks of follow-up, as did lean body mass and whole body bone mineral content. Whereas four people had a viral load below 50 copies/mL when the study started, six loads lay below the 50-copy mark 12 months later. HDL cholesterol edged up (from 43 to 46 mg/dL) and LDL cholesterol inched down (from 142 to 135 mg/dL)—both nonsignificant changes—while triglycerides dwindled nonsignificantly from 360 to 247 mg/dL ($p = 0.152$). All mean weight and fat measures improved with 12 months of TDF, and all fat gains except in the leg were statistically significant:

- Weight: 68.2 to 71.7 kg ($p = 0.011$)
- Body mass index: 22.56 to 23.71 kg/m^2 ($p = 0.011$)
- Total fat: 12.4 to 16.1 kg, +30.0 percent ($p = 0.004$)
- Total fat percent: 17.7 to 21.63 percent ($p = 0.004$)
- Arm fat: 1.2 to 1.7 kg, +41.3 percent ($p = 0.027$)
- Leg fat: 2.2 to 2.9 kg, +33.2 percent ($p = 0.086$)
- Limb fat: 3.4 to 4.6 kg, +43.1 percent ($p = 0.026$)
- Trunk fat, 8.5 to 11.0 kg, +28.2 percent ($p = 0.002$)

TDF's beneficent imprint on fasting lipid profiles held true in a much larger cohort study comparing 319 people taking antiretrovirals (including 117 taking TDF) and 138 untreated HIV-infected individuals [abstract 106]. In multivariate analyses adjusted for gender, lipoatrophy, lipohypertrophy, body mass index, and antiretroviral use, Stefan Mauss (Center for HIV and Hepatogastroenterology, Düsseldorf) and colleagues in other cities tied TDF to significantly lower total cholesterol, triglycerides, very low-density lipoprotein (VLDL) cholesterol, and VLDL triglycerides. None of the other NRTIs analyzed—AZT, ddI, d4T, 3TC, or ABC—correlated

with these improvements. But AZT-containing regimens favored higher HDL cholesterol in multivariate analysis.

All of the PIs studied except ATV earned at least one black mark in these lipid audits, while both nevirapine (NVP) and EFV regimens favored higher total and LDL cholesterol. The analyses also linked NVP to higher HDL cholesterol. Age over 49 years—never a good thing in studies like this—favored significantly higher total, LDL, and VLDL cholesterol. And people lugging a body mass index above 29 kg/m^2 had significantly higher total and LDL cholesterol.

In the published three-year randomized comparison of treatment-naive people starting TDF or d4T (with 3TC and EFV), triglycerides, total cholesterol, and LDL cholesterol all rose significantly more in the d4T group, while HDL cholesterol climbed significantly more in the TDF group.[14] Trial clinicians chalked up nine cases of lipodystrophy among 299 people randomized to TDF (3 percent) versus 58 among 301 assigned to d4T (19 percent) ($p < 0.001$).

ATV, RTV, insulin resistance, and lipids

Indinavir (IDV) upsets glucose metabolism, but clinical trials of ATV turned up little evidence of askew glucose. Some work blames IDV blockade of the glucose transporter GLUT4 for these problems, while cell studies suggest ATV leaves GLUT4 alone. But stymied GLUT4 did not figure in the insulin resistance acutely induced by a single dose of IDV/RTV, reported Dominic Doran (John Moores University, Liverpool) [abstract 6]. The same study found that RTV-boosted ATV has no immediate impact on glucose metabolism.

Doran rounded up 18 hale young men without HIV who volunteered not only to endure euglycemic hyperinsulinemic clamping after biking for 60 minutes at 70 percent VO$_2$max (maximum volume of oxygen consumed), but also to sit still for three muscle biopsies—one before the experiment began, a second 60 minutes after taking PIs or placebo, and a third after the stationary bike stint. He randomized six men to take 800/100 mg of IDV/RTV, six to take 300/100 mg of ATV/RTV, and six to take placebo.

The clamp test showed significantly lower insulin-mediated glucose disposal in the IDV/RTV group than in either other group:

- IDV/RTV: 8.19 ± 0.3 mg/kg/min per μU/mL
- ATV/RTV: 12.1 ± 1.0 mg/kg/min per μU/mL ($p < 0.05$)
- Placebo: 14.58 ± 1.0 mg/kg/min per μU/mL ($p < 0.05$)

The nonoxidative part of total glucose disposal—reflecting glucose storage—also proved sharply lower with IDV/RTV than with ATV/RTV or placebo:

- IDV/RTV: 3.74 ± 0.42 mg/kg/min
- ATV/RTV: 5.62 ± 0.60 mg/kg/min ($p < 0.01$)
- Placebo: 5.40 ± 0.53 mg/kg/min ($p < 0.01$)

But the groups did not differ in levels of total GLUT4 mRNA or protein.

Doran concluded that IDV/RTV rapidly blocks glucose use by slicing glycogen storage, while ATV/RTV does not. Steven Grinspoon (Massachusetts General Hospital, Boston) cautioned that the results may not have an exact fit in people with HIV, who typically differ from healthy young men in fat buildup, free fatty acid ramblings, and so on. He did not think Doran's data rule out subtle insulin interference by low-dose RTV in HIV-infected people.

In studies of human fat and liver cells, Mustafa Noor (Bristol-Myers Squibb) found no difference in cholesterol or triglyceride synthesis when comparing ATV alone with ATV/RTV [abstract 43]. In the same experiments LPV/RTV hiked triglyceride synthesis in liver cells (increasing triglyceride production), while blunting its synthesis in fat cells (decreasing its storage). Noor suggested his findings mean that an RTV boost won't botch ATV's laissez-faire liaison with lipids, though he called for clinical confirmation.

Lipid and fat changes with 120 weeks of FPV/RTV

Two years of follow-up revealed few fat changes in 211 treatment-naive people starting 1,400/200 mg of FPV/RTV plus

Table 4. **Fat changes in people taking FPV/RTV for 120 weeks***			
	Any body fat change (%)	Any fat wasting (%)	Any fat accumulation (%)
Week 48	34 of 180 (19)	8 of 188 (4)	32 of 195 (17)
Week 96	32 of 160 (20)	8 of 165 (5)	32 of 173 (18)
Week 120	29 of 156 (19)	8 of 161 (5)	31 of 166 (19)

*Including only those with no reported fat abnormality before treatment.
Source: Sharon Walmsley, abstract 50.

3TC/ABC. The same people enjoyed a 35 percent spurt in HDL cholesterol in 120 weeks of scrutiny.

Sharon Walmsley (Toronto Hospital University Health Network) and colleagues in Frankfurt charted body fat changes logged by physicians on a standardized form before treatment began, at weeks 24 and 48, then every 12 weeks [abstract 50]. The 152 men and 59 women in the fat-change study group started FPV/RTV at a relatively young median age of 36 years, with median RNA and CD4 numbers at 4.82 log copies/mL (about 66,000 copies/mL) and 168 cells/mm^3. Forty-five (21 percent) had AIDS. More than 80 percent stayed with 3TC/ABC from week 48 through week 120.

Only two people stopped the regimen because of lipodystrophy. The prevalence of lipoatrophy and lipohypertrophy rose over the first 48 weeks of treatment, then varied hardly at all through week 120 (Table 4). People who began treatment with a CD4 count under 200 cells/mm^3 or a viral load topping 100,000 copies/mL had more fat wasting before treatment than did people with less advanced HIV disease. But physician reports indicated a dwindling prevalence of lipoatrophy in this group as follow-up continued.

From this group of 211 people, 125 men and 49 women had fasting lipids measured before treatment and at weeks 48, 96, and 120 [abstract 99]. Total cholesterol rose from a pretreatment median of 162 mg/dL to 215 mg/dL at week 48, 209 mg/dL at week 96, and 213 mg/dL at week 120. That initial rise and subsequent plateau reflected similar changes in HDL and LDL cholesterol. The total-to-HDL cholesterol ratio jumped from 4.4 to 4.8 through week 48, then returned to baseline at weeks 96 and 120. The proportion of people with an ominously low HDL

reading—under 40 mg/dL—dropped from 62 percent at baseline to 36 percent at week 48, 27 percent at week 96, and 31 percent at week 120.

From week 48 to week 120, one person had grade 3 or 4 cholesterol gains and seven had grade 3 or 4 triglyceride romps. Only two people abandoned the regimen because of dangerously errant lipids—high triglycerides in both cases. The findings suggest that RTV boosting of FPV puts less pressure on lipids than RTV boosting of lopinavir (LPV).

DON'T GIVE UP ON DIETING

The impact of diet and exercise on fat changes and peripatetic lipids remains hard to study in a controlled way. Getting people to diet and exercise isn't easy either. Perhaps these difficulties explain the perennial paucity of diet and exercise studies in people suffering antiretroviral devilry. Exercise can accent the popped-muscle look of lipoatrophy; otherwise well-planned exercise and dieting have few if any ill effects and many wholesome ones.

A study by Vanessa Carter (The Alfred, Melbourne) offered more proof that diet alone can ease high lipids in people taking antiretrovirals [abstract 77]. But it also confirmed that many antiretroviral-treated people need antilipid drugs as well.

The retrospective analysis involved 40 people referred to a multidisciplinary clinic aimed at hemming heart disease risks. Most of them, 37, got referred for unruly lipids, though referral reasons included lipodystrophy in four people, diabetes in two, and overweight in two. Upon entering the clinic these 38 men and two women averaged 47 years in age, 24.3

kg/m^2 in body mass index, and 88.9 cm in waist width. After two years of follow-up, body mass index and girth did not change.

In their first clinic visit 26 people got only dietary mandates, while 14 got dietary advice plus a medication change. Two years later, only eight people remained solely on dietary therapy, while the 32 others followed both diet and drug regimens to address their problems. At the end of follow-up the Alfred clinicians had prescribed a statin for 21 people, fish oil for 11, and a fibrate for eight. Nineteen people also changed at least one antiretroviral.

Among people who stuck to dieting alone, total cholesterol fell significantly from a collective 7.5 to 6.4 mmol/L ($p = 0.015$). Triglycerides also dropped, from 4.1 to 3.2 mmol/L, a nonsignificant change. In the group treated with both diet and drugs, both total cholesterol and triglycerides fell significantly—cholesterol from 7.7 to 6.3 mmol/L ($p = 0.028$) and triglycerides from 5.2 to 3.8 mmol/L ($p = 0.01$). Not surprisingly, baseline levels of both lipids stood higher in the group that needed lipid lowerers to abet their diet. Along the way, clinic staff persuaded four of 17 smokers to stop.

All these measures combined to lower the group's cardiovascular disease risk from 12 percent to 7 percent on the Framingham scale. That drop eased the group from the moderate-to-high risk bracket (10 to 20 percent) into the low-to-moderate risk echelon (under 10 percent).

Meanwhile, research in the non-HIV world confirmed the value of moderate exercise in battling the metabolic syndrome—an unholy alliance that may include excess abdominal fat and high blood pressure, glucose, or cholesterol.[41] Anywhere from 25 to 40 percent of people living in the United States—including lots with HIV—have the metabolic syndrome.

Johns Hopkins University researchers randomized 104 people between 55 and 75 years old to six months of supervised drills including weight lifting and cardio workouts or to a control group that got a booklet encouraging exercise. No one had a history of heart disease.

Aerobic fitness rose 16 percent in the exercise group, while muscle strength climbed 17 percent. Exercisers shed 20

Table 5. **Change in cheek thickness with lipoatrophy procedures**

	Fat transfer (mean mm ± SD)	Polylactic acid (mean mm ± SD)	Polyacrylamide (mean mm ± SD)	p
n	24 (15 M; 9 W)	20 (14 M; 6 W)	15 (12 M; 3 W)	
Week 0	5.8 ± 2.6	4.9 ± 2.7	3.9 ± 2.9	<0.001
Week 24	9.7 ± 3.9	8.8 ± 3.9	8.4 ± 2.4	0.352
Change	3.3 ± 4.1	3.5 ± 4.0	2.1 ± 3.0	0.687

Source: Giovanni Guaraldi, abstract 12.

percent of their abdominal fat. Total cholesterol, HDL cholesterol, VLDL cholesterol, triglycerides, and insulin sensitivity all improved in the exercise group. As a whole the control group did not enjoy these changes. The Johns Hopkins team charted no new cases of metabolic syndrome in the exercise group, and nine cases resolved, for an overall drop of 47 percent. The syndrome resolved in eight people in the control arm, but it developed in four people, for an overall drop of only 18 percent.

CALL THE SURGEON

For people with HIV surgery can be a face-saver and a life-saver—literally, in both cases. Giovanni Guaraldi (University of Modena, Italy) offered the first (quasi) randomized look at three surgical options for facial atrophy, and Franck Boccara (Saint-Antoine Hospital, Paris) deciphered coronary artery bypass graft (CABG) outcomes in two HIV cohorts.

Three fixes for facial atrophy
The facial atrophy study involved 41 men and 18 women with severe lipoatrophy while taking a stable antiretroviral regimen [abstract 12]. Everyone had a CD4 count above 100 cells/mm^3, and surgeons could exclude anyone they thought would not benefit from surgery. People with enough fat for autologous transfer underwent that procedure with Coleman's technique; Guaraldi and colleagues randomized the others to injections of resorbable polylactic acid (PLA, New-Fill, Sculptra) or nonresorbable polyacrylamide (PAC). The median number of injections needed with PLA (five) and PAC (six) did not differ significantly.

Six months after the procedures, Guaraldi compared ultrasound scans of subcutaneous plus dermal thickness of the right cheek

with baseline scans. Although people who had self-fat transfers had significantly thicker cheeks before treatment, the groups did not differ in 24-week results or in change from baseline to week 24 (Table 5).

Subjective satisfaction measured on a visual analog scale did suggest better results with the injections (mean 83 for both PLA and PAC) than with fat transfer (mean 70) ($p = 0.007$). The change in scores from week 0 to week 24 showed a trend toward higher satisfaction with PLA (mean 51) and PAC (mean 57) than with fat transfer (mean 38) ($p = 0.075$).

Four of 24 people who had fat transfers ended up with the chubby-cheek "hamster syndrome," which Guaraldi noted can prove incorrigible. Three of those four had fat transferred from a buffalo hump, a technique the group has abandoned. Eight of 20 people in the PLA group had subcutaneous nodules. No one who got PAC shots had any problem. Guaraldi observed that six months of follow-up is not enough to compare the durability of these procedures.

Rerouting coronary arteries
Coronary artery bypass grafting has become routine in wealthier lands. Even if antiretrovirals did not ratchet up the risk of clogged arteries, the aging of HIV-infected populations would guarantee a growing list of retrovirus-ridden CABG candidates. How do people with HIV do after arterial cutting and pasting? Franck Boccara's case-control study afforded some insight [abstract 115].

The comparison involved 19 people with HIV and 38 age- and gender-matched controls who had bypass surgery from 1997 through 2003 at Saint-Antoine Hospital in Paris or La Sapienza University in Rome. Ages averaged 48.3 years in the HIV group and 49.5 among controls. All but one person with HIV (and hence all but

two controls) were men. Significantly more people with HIV had high triglycerides, and significantly more without HIV were obese. Otherwise cases and controls matched closely. Each group needed an average 2.7 grafts.

CD4 counts fell significantly in the HIV group, but not dangerously (481 ± 165 to 410 ± 156 cells/mm^3), while the group's viral load barely budged from 195 to 215 copies/mL. No one in the HIV or non-HIV group died around the time of surgery, and perioperative clinical setbacks were evenly divided — one myocardial infarction in the HIV group, one stroke among the controls, two cases of sepsis with HIV and seven without, and one case of bleeding in each group. Two control patients needed an early repeat CABG.

After a median 29 months of follow-up on 18 cases and 38 controls, however, Boccara recorded significantly more reversals in the HIV group. One person with HIV, and none without HIV, died. Eleven people with HIV (58 percent) either died from cardiovascular disease, had a myocardial infarction, or needed another CABG, compared with seven controls (18 percent) ($p = 0.002$).

Boccara concluded that CABG is a "safe and reasonable" procedure for HIV-infected people with multivessel disease. But they endure more cardiovascular mishaps in the first two years after surgery than do people without HIV.

INSULIN RESISTANCE

Enzo Bonora's ongoing analysis of the Bruneck cohort confirms that insulin resistance is an independent risk factor for cardiovascular disease, he told workshop attendees. And hefty proportions of people with HIV now have insulin resistance. Several studies link PIs — with the possible exception of ATV and amprenavir (APV) — to insulin resistance. And switching from a PI to ABC, NVP, or (less consistently) EFV may reverse the problem. But these drugs are not prescribed in a vacuum, so what role do other NRTIs play?

To cipher the insulin-specific impact of all antiretrovirals, Todd Brown (Johns Hopkins University, Baltimore) compared 533 HIV-infected men in the Multicenter AIDS Cohort Study (MACS) with 755 uninfected MACS members [abstract 10]. The control group was older (median 50 versus 46 years), heavier (median 26 versus 25 kg/m^2), and whiter (88 versus 81 percent) than the HIV group ($p < 0.001$ for all comparisons). Significantly more men with HIV had HCV coinfection (5 versus 1 percent, $p < 0.001$) or a family history of diabetes (42 versus 35 percent, $p = 0.005$), but neither of these factors independently inflated the risk of insulin resistance. The median nadir CD4 count of the HIV group measured 248 cells/mm^3.

Brown divided the HIV contingent into those who never took antiretrovirals and those treated most recently with single or double NRTIs, a potent non-PI regimen, or a potent PI combo. Compared with the control group, every HIV group had a higher risk of high insulin (above 15 μU/mL) and a lower (worse) QUICKI-calculated insulin resistance score (1/log glucose + log insulin):

- Naive: odds ratio (OR) 1.72 for insulin resistance, QUICKI 0.27 lower than controls
- NRTIs only: OR 1.89 for insulin resistance, QUICKI 0.45 lower than controls
- Non-PI regimen: OR 2.64 for insulin resistance, QUICKI 0.57 lower than controls
- PI regimen: OR 4.05 for insulin resistance, QUICKI 0.68 lower than controls

Surveying cumulative treatment with each antiretroviral class, Brown found the highest risk of hyperinsulinemia and the greatest (worst) QUICKI differential with longer NRTI exposure. Compared with controls the odds ratio for insulin readings above 15 μU/mL measured 1.12 (95 percent confidence interval [CI] 1.07 to 1.17) per year of NRTI therapy versus 1.07 (95 percent CI 1.00 to 1.14) per year of PI therapy. Each year of NNRTI therapy appeared to trim the risk of lofty insulin (OR 0.96, 95 percent CI 0.86 to 1.08).

Similarly, each added year of NNRTI therapy opened no gap in QUICKI scores compared with the control group. But every extra year of NRTI treatment shaved 0.06 off the QUICKI score compared with controls. Each extra year of PI therapy opened only a 0.01 QUICKI difference from controls.

When Brown turned his attention to individual drugs, he linked three with a higher risk of an insulin tab above 15 μU/mL: IDV (OR 1.14 for each additional year of treatment), 3TC (OR 1.12 for each year), and d4T (OR 1.22 for each year).

Because HIV infection itself raised the risk of insulin resistance, sorting out the cumulative or discrete contribution of classes and drugs is challenging. For example, two earlier studies tied IDV to insulin resistance in people with[42] or without[43] HIV. Similar research in people without HIV linked LPV/RTV to unruly insulin.[44] But LPV may have survived Brown's analysis because fewer people would have used that PI than used IDV during the April 1999 to April 2003 study period. By the same token the popularity of d4T/3TC during the study window may weigh against those nucleosides in such an analysis. Brown and MACS colleagues adjusted their analyses for age, body mass index, race, nadir CD4 count, HCV status, and family history of diabetes, but not for duration of HIV infection.

Insulin resistance — as well as endothelial dysfunction — may lie behind the high rate of pre-eclampsia reported in antiretroviral-treated women, a Barcelona group suggested [abstract 23]. At the 2003 Lipodystrophy Workshop these clinicians found a 12 times higher risk of pre-eclampsia (pregnancy-induced hypertension and proteinuria) in women with HIV than in uninfected women.[45] At this year's workshop, Ana Milinkovic (University Hospital Clinic, Barcelona) offered a case-control comparison of nine HIV-infected antiretroviral-treated women with pre-eclampsia and nine HIV-infected pregnant women without pre-eclampsia.

The pre-eclampsia group had significantly higher levels of P selectin, an endothelial dysfunction marker, than did controls at the estimated time of conception, during pregnancy, and in the days after delivery. During pregnancy the women who later had pre-eclampsia had significantly higher insulin levels than control women (36.0 ± 33.2 versus 9.4 ± 6.5 mU/L) ($p = 0.031$).

Table 6. Bivariate predictors of bone loss in a VA cohort

	With bone loss	Without bone loss	p
Caucasian (%)	21	35	0.054
African American (%)	68	56	
Other (%)	10	10	
Mean days with undetectable viral load ± SD	1,030 ± 767	1,272 ± 833	0.019
Mean body mass index (kg/m^2) ± SD	25 ± 4	27 ± 3	0.001

SD = standard deviation.
Source: Aronson et al.[48]

Simon Mallal's group at the Royal Perth Hospital showed three years ago that genetic testing can pick out people at high risk of hypersensitivity to ABC—at least in white populations like the one studied in Perth.[46] Although genetic screening hasn't crossed the threshold into everyday practice, patch tests and CD4 assays have. Two groups showed that these quotidian touchstones may help spot ABC hypersensitivity.

Clinical clues to ABC hypersensitivity

With colleagues in Perth and Liverpool, Elizabeth Phillips (University of Toronto) compared patch test results and other findings in seven people who had an earlier positive hypersensitivity patch test and 11 controls who tolerated ABC [abstract 8]. All seven people with earlier positive patches had strongly positive reactions 10 to 45 months after their first test. They did not differ from controls in CD4-cell cytokine production or proliferation. But in five of the original seven—versus one of 11 controls—ABC spawned faster CD8-cell breeding ($p = 0.005$). And CD8s spilled interferon gamma in two of seven cases but in none of 11 controls ($p = 0.04$). HLA-B*5701, the genetic hypersensitivity harbinger, turned up in all seven cases and one of 11 controls ($p < 0.001$).

The strong link between positive patch testing, HLA-B*5701, and CD8 responses suggested to Phillips that HLA-B*5701-restricted CD8 T cells mediate ABC hypersensitivity. She cautiously proposed that "clinical, genetic and immunological tests may have complementary application in the prevention, diagnosis and management" of ABC hypersensitivity. The study also showed that patch testing is safe in people hypersensitive to ABC. Even those with the most florid patch test flares had no systemic reaction. These researchers now wonder whether negative patch tests can identify people who carry HLA-B*5701 yet tolerate ABC.

Just after the Lipodystrophy Workshop, a group from Cleveland's Case Western Reserve University lighted on a way to foretell ABC hypersensitivity in people who just started the drug—sudden abstruse downturns in CD4 and CD8 cells.[47] Exploiting this hypersensitivity semaphore may not be clinically practical because it would require intense CD4 monitoring. But a fortuitously measured CD4 drop could flag the reaction in some people.

The Case Western team noticed T-cell tail-offs in five people enrolled in a study of ABC, AZT, and 3TC with or without EFV and cyclosporine. Unexplained drops in CD4s and CD8s appeared before or with hypersensitivity symptoms, which erupted four to 22 days after people started ABC. These were not petite dips in T-cell tallies. The CD4 plunge averaged 166 cells/mm^3 (range 110 to 322 cells/mm^3), and the average CD8 drop measured 465.2 cells/mm^3 (range 298.5 to 717.5 cells/mm^3). Total lymphocytes walked off a 754-cell cliff (range 465 to 1,520 cells/mm^3), and white cell counts shrank an average 350 cells/mm^3 but rose in some people (range -1,115 to +4,100 cells/mm^3).

These T-cell decays did not mirror viral load rebounds, a drop in platelets, or blood disorders. And they did not correlate with the severity of hypersensitivity, time on ABC, or use of other drugs including cyclosporine, EFV, or trimethoprim-sulfamethoxazole. As soon as people stopped ABC, the counts swung back to previous levels.

The researchers ventured that their findings "might represent cellular redistribution [out of the peripheral circulation and] to the areas affected by the inflammatory response." The quick rebound in circulating T cells after people quit ABC fits that theory.

Bone thinning in African Americans

HIV-linked bone thinning may be more common among African-American men than white men, according to results of a US Veterans Affairs (VA) study.[48] Taking PIs appeared to protect against bone loss in this analysis, unveiled just after the Lipodystrophy Workshop.

The study involved 272 HIV-infected active members of the military, veterans, and their dependents, most of them men (84 percent) and most African American (62 percent). The cohort was light in smokers (14 percent) and drinkers (12 percent swigged more than two drinks a day). They had a high mean CD4 count of 539 cells/mm^3 and were relatively young, averaging 44 years among whites, 41 years among Hispanics, and 40 years among African Americans.

Defining bone loss as osteopenia or osteoporosis determined by World Health Organization criteria and measuring bone density by DEXA scans, the VA researchers linked bone loss to African-American race, a longer time with an undetectable viral load, and lower weight (Table 6).

In this analysis PI therapy did not predict bone loss. Neither did gender, age, mean duration of HIV infection or antiretroviral therapy, mean days with a CD4 count under 50 cells/mm^3, lowest-ever CD4 count, current CD4 count, or smoking. Classic bone loss beacons—steroid use, wasting, smoking, drinking, thyroid disease, and hypogonadism—were rare in this population and did not correlate with thin bones.

African Americans proved 1.7 times more likely than others to have any bone loss (95 percent CI 1.1 to 2.9) in a multivariate model tweaked to consider smoking. When researchers confined the analysis to spine density, African Americans had a 2.3 times higher risk of bone loss (95 percent CI 1.3 to 3.8). A model adjusted for smoking
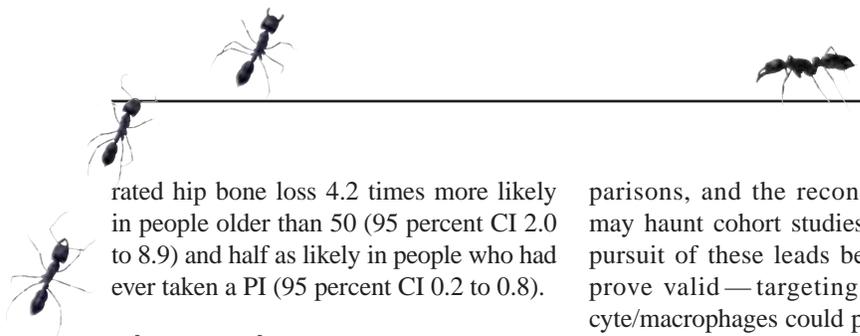
rated hip bone loss 4.2 times more likely in people older than 50 (95 percent CI 2.0 to 8.9) and half as likely in people who had ever taken a PI (95 percent CI 0.2 to 0.8).

Why wasting hasn't gone away

Despite the benisons of today's benchmark regimens, some people with HIV still lose muscle mass. Two research teams proffered divergent reasons for this seeming anachronism:

- Cytokine-driven disruption of metabolism
- HIV-driven apoptosis of skeletal muscle

The first hypothesis came from Cecilia Shikuma (University of Hawaii), who proposed that potent antiretrovirals permit low-level replication in monocyte/macrophages, which dump cytokines that derange normal metabolism [abstract 57]. To test this theory she reckoned proviral DNA levels in peripheral blood mononuclear cells (PBMCs) of 57 people who did or did not suffer 5 percent or more weight loss over one year of follow-up.

Baseline viral load or CD4 count did not differ between 11 people who lost weight and the 46 with stable or increasing weight. But Shikuma recorded significantly higher proviral DNA numbers in PBMCs from the weight-loss group—8.9 versus 0.9 copies/million cells ($p = 0.006$). When she limited the analysis to people with plasma RNA quotients below 50 copies/mL, the people who lost weight still had significantly more proviral DNA in PBMCs—8.9 versus 0.5 copies/million cells ($p = 0.028$). Homing in on the proviral DNA cache in two people with the highest levels, she found more than 99 percent in activated monocyte/macrophages.

But one piece of the puzzle didn't quite fit. In a subset of people who had plasma cytokine levels measured, Shikuma found no difference between the weight-loss and stable-weight groups in interleukin (IL-)6, IL-8, IL-10, soluble TNF receptor type 1 or 2, or soluble FAS. She did see a correlation between macrophage chemotactic protein 1 and weight loss (Pearson correlation 0.659, $p = 0.003$).

Shikuma cautioned that the analysis has clear shortcomings—the small sample, the lack of adjustment in multiple com-

parisons, and the recondite biases that may haunt cohort studies. But she urged pursuit of these leads because—if they prove valid—targeting HIV in monocyte/macrophages could plug the cytokine leaks that may promote muscle wasting.

Sònia López (University Hospital Clinic, Barcelona) took a different tack in her pursuit of wasting's workings since the dawn of potent therapy [abstract 29]. She snipped deltoid muscle samples from the nondominant arms of 18 healthy volunteers and five people with HIV but no symptoms and no antiretroviral history. To gauge proportions of apoptotic cells, she stained them with appropriate markers and turned them over to three independent technicians who didn't know their origins.

Calculating an apoptotic index as total apoptotic muscle cell nuclei divided by total muscle cell nuclei times 100, she figured an 80 percent index in the HIV group versus 0 percent in controls ($p < 0.01$). How HIV may incite muscle-cell suicide remains unknown.

"Our most-feared nightmare"

Brandishing real-time PCR and high-tech TUNEL assays to tease out reasons for wasting, as in the just-outlined studies, is strictly a Western pursuit. In countries that still count tiny percentages of antiretroviral-treated people, wasting's causes are the same as ever—runaway opportunists, malabsorption, malnutrition, sometimes even famine. Though access to antiretrovirals remains painfully, mortally constrained in most places with the greatest need, the tide has at least turned. Yet even this therapeutic trickle has raised a toxic specter that may well play out differently in poor countries, workshop attendees heard from Elly Katabira (Makerere University, Kampala, Uganda).

The scope of Africa's HIV problem may still escape some in the West, but Katabira brought the sub-Saharan epidemic swiftly into focus with one astounding statistic: People with HIV fill 75 percent of Uganda's urban hospital beds. Among those lucky enough to get antiretrovirals, the risk of toxicity is high because many have acutely advanced disease. Feeling sicker after starting these drugs—heralded as miracle balms—promptly erodes confi-

dence and so threatens poor adherence and resistance. Too many poor responses, Katabira fears, could fuel publicity of antiretroviral toxicity, derail scaling-up efforts, and defeat voluntary counseling and testing.

The immune reconstitution syndrome—so common in people with TB—poses a particular threat, according to Katabira. People who suffer the syndrome, and poorly trained clinicians who treat them, naturally want to stop therapy immediately.

Katabira's warning was blunt: "Persistence [of toxicity] is likely to undermine the accelerated efforts to increase the use of antiretrovirals in the developing world. This," he added, "is our most-feared nightmare." ∎

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Racial and gender disparities in receipt of highly active antiretroviral therapy persist in a multistate sample of HIV patients in 2001

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BACKGROUND: National data from the mid-1990s demonstrated that many eligible patients did not receive highly active antiretroviral therapy (HAART) and that racial and gender disparities existed in HAART receipt. We examined whether demographic disparities in the use of HAART persist in 2001 and if outpatient care is associated with HAART utilization. METHODS: Demographic, clinical, and pharmacy utilization data were collected from 10 US HIV primary care sites in the HIV Research Network (HIVRN). Using multivariate logistic regression, we examined demographic and clinical differences associated with receipt of HAART and the association of outpatient utilization with HAART. RESULTS: In our cohort in 2001, 84 percent of patients received HAART and 66 percent had four or more outpatient visits during calendar year (CY) 2001. Of those with two or more CD4 counts below 350 cells/mm in 2001, 91 percent received HAART; 82 percent of those with one CD4 test result below 350 cells/mm received HAART; and 77 percent of those with no CD4 counts below 350 cells/mm received HAART. Adjusting for care site in multivariate analyses, age >40 years (adjusted odds ratio [AOR] = 1.13), male gender (AOR = 1.23), Medicaid coverage (AOR = 1.16), Medicare coverage (AOR = 1.73), having one or more CD4 counts less than 350 cells/mm (AOR = 1.33), and having four or more outpatient visits in a year (OR = 1.34) were significantly associated with an increased likelihood of HAART. African Americans (odds ratio [OR] = 0.84) and those with an injection drug use risk factor (OR = 0.86) were less likely to receive HAART. CONCLUSIONS: Although the overall prevalence of HAART has increased since the mid-1990s, demographic disparities in HAART receipt persist. Our results support attempts to increase access to care and frequency of outpatient visits for underutilizing groups as well as increased efforts to reduce persistent disparities in women, African Americans, and injection drug users (IDUs).

Emergence of antiretroviral resistance in HIV-positive women receiving combination antiretroviral therapy in pregnancy

Lyons FE, Coughlan S, Byrne CM, et al.

BACKGROUND: Antenatal antiretroviral therapy is integral to preventing vertical transmission of HIV-1. The impact of temporary triple antiretroviral therapy in pregnancy on the emergence of antiretroviral resistance has not been studied. OBJECTIVE: To determine the impact of temporary triple antiretroviral therapy in pregnancy on emergence of antiretroviral resistance. METHODS: Pregnant HIV-1 infected women with a pre-treatment CD4 cell count >300 x 10^1 initiated triple antiretroviral therapy in the third trimester and discontinued postpartum. Genotypic resistance testing was performed after antiretroviral cessation and on pretreatment samples when postpartum samples showed primary mutations. RESULTS: In a cohort of 50 women who initiated antiretroviral therapy in pregnancy, 39 (78 percent) had postpartum HIV-1 nucleotide sequences available for analysis: 35 of these (90 percent) were previously antiretroviral naive. Seven primary mutations, V106A (one), Y181C (two), G190A (one), K101E (one), M184V (one), T215S (one) were detected in five (13 percent) women. All five were on regimens that included nevirapine and all were antiretroviral therapy naive prior to the index pregnancy. Four had no mutations detected pretreatment (one did not have a pretreatment analysis available; viral load 83 copies/ml). The median duration of antiretroviral exposure was 70 days. CONCLUSION: Emergence of genotypic resistance is significant in this cohort of pregnant women. All mutations detected were in those that took nevirapine-containing regimens. The clinical implications of these mutations are unknown.

Understanding the role of HIV load in determining weight change in the era of highly active antiretroviral therapy

Mwamburi DM, Wilson IB, Jacobson DL, et al.

BACKGROUND: In this prospective cohort study, we determined the relationship between human immunodeficiency virus (HIV) RNA load and body weight in patients with HIV infection. METHODS: Repeated-measures analysis was restricted to patients with two or more study visits, four- to nine-month intervals between study visits, and complete data on virus load, resting energy expenditure (REE), and highly active antiretroviral therapy (HAART). The outcome was change in body weight across study intervals. The main predictor was virus load. Separate analyses were performed for weight change in patients receiving and patients not receiving HAART. RESULTS: The eligible sample consisted of 318 participants associated with 1,886 study intervals. Sixty-one patients (19 percent) were women, and 173 (54 percent) were undergoing HAART at the time of enrollment. There was a significant interaction ($p = 0.01$) between virus load and HAART use. In the absence of HAART, each $\log_{10}$ increase in virus load was associated with a 0.92-kg decrease in body weight ($p = 0.003$), but during HAART, virus load was not significantly associated with weight change. During HAART, a CD4 count decrease of 100 cells/mm^3, rather than a change in the virus load, was associated with a 0.35-kg decrease in body weight ($p < 0.001$). REE was independently associated with weight change in both models ($p < 0.001$). CONCLUSIONS: Patients with HIV infection who are losing weight and are not taking HAART should be considered for HAART. Patients who are already receiving HAART and have unsuppressed virus loads may benefit virologically from an intensified regimen, because such a regimen may lead to complete suppression if there is an accompanying increase in CD4 counts. Further research is needed to understand the strong independent effect of changes in REE among patients receiving and patients not receiving HAART.

Metabolic syndrome among HIV-infected patients: Prevalence, characteristics, and related factors

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OBJECTIVE: To assess the prevalence in HIV-infected patients of the metabolic syndrome as defined by the National Cholesterol Education Program (ie, three or more of the following components: abdominal obesity, hypertriglyceridemia, low HDL cholesterol, high blood pressure, and high fasting glucose). RESEARCH DESIGN AND METHODS: In this cross-sectional study, 710 HIV-infected patients managed at the outpatient clinic of a tertiary hospital during 2003 completed the study protocol consisting of a medical examination and laboratory analysis after a 12-hour overnight fast. RESULTS: Metabolic syndrome prevalence was 17 percent and increased from 5.1 percent among HIV-infected patients under age 30 years to 27.0 percent for those aged 50-59 years. Age (per 10-year increment) (odds ratio [OR] 1.41 [95 percent CI 1.12-1.77]), BMI (1.27 [1.19-1.36]), past and present protease inhibitor exposure (2.96 [1.03-3.55] and 4.18 [1.4-12.5], respectively) were independently associated with the metabolic syndrome on logistic regression analysis. Furthermore, only stavudine (d4T) (1.74 [1.01-2.98]) and lopinavir/ritonavir (2.46 [1.28-4.71]) were associated with the metabolic syndrome after adjustment for age and BMI. CONCLUSIONS: The prevalence of metabolic syndrome among these HIV-infected patients is similar to that previously reported in uninfected individuals. Of specific concern is the association of protease inhibitor exposure with the metabolic syndrome and, more specifically, with exposure to stavudine and lopinavir/ritonavir when individual antiretroviral drugs were analyzed.
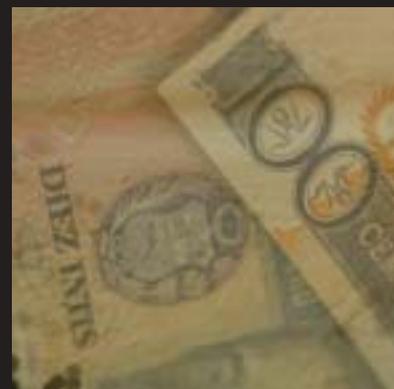
IAPAC, with its broad mission to improve the healthcare of all who have been affected by the AIDS pandemic, is working to ease suffering and to ensure that persons living with HIV/AIDS are able to live productive lives. Though the battle ahead is one requiring the greatest of global commitments, even small donations from concerned world citizens with the means to provide a small amount of financial assistance can make a notable impact.

The same poverty that engenders higher infection rates in the developing world also means an inadequacy of healthcare infrastructure and, often, the inability of physicians and allied health professionals to access the training and information that they require to effectively treat those in their care.

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With your donation of US$60 (or more), you can help IAPAC in its mission as an agent of change. For only US$60, IAPAC can sustain the cost of an annual membership for a physician in the developing world, thus enabling physicians in the regions most heavily burdened by HIV disease to gain greater access to critical clinical and policy information and to more fully partake of specialized HIV/AIDS medical training provided in the countries where it is most needed.

For additional information on how you can make a difference, contact Joey Atwell, Director of Membership, at (312) 795-4941 or jatwell@iapac.org, or complete and submit an on-line application at www.iapac.org.

Multiple HCV genotype infection speeds HIV progression

Liz Highleyman

Concurrent infection with more than one genotype of hepatitis C virus (HCV) is associated with more rapid HIV disease progression, according to a European study published in the journal *AIDS*.[1]

HIV/HCV coinfection has been linked to more rapid liver disease progression, but its effect on the course of HIV disease progression remains controversial and recent studies have yielded conflicting data. One possible reason for these disparate results is that the effect of hepatitis C on HIV disease progression may vary by HCV genotype.

Researchers with the European Seroconverter Study and the Italian Seroconverter Study analyzed data from 126 HIV/HCV-coinfected injecting drug users from seven European countries—Austria, France, Italy, The Netherlands, Scotland, Spain, and Switzerland—with known dates of HIV infection. About two thirds (68 percent) were male, and the average age at HIV seroconversion was 27 years.

Participants' HCV genotypes were determined early in the course of HIV infection. Genotype 1 was most common (48 percent), followed by genotype 3 (34 percent), genotype 4 (13 percent), and genotype 2 (1 percent); 5 percent were infected with more than one HCV genotype (one subject with 1b and 3a; four with 1b and 4; and one with 3a and 4). None of the participants were receiving treatment for hepatitis C.

The researchers analyzed the effect of highly active antiretroviral therapy (HAART), which became available between March 1996 and September 1996 (depending on study site). By July 1997, 60 percent of subjects had started HAART. That percentage increased to 75 percent by January 1999.

Participants with missing CD4 cell measurements or with CD4 counts <200 cells/mm^3 at baseline were excluded from the analysis of immunological progression, leaving data from 108 subjects. After a median follow-up period of 7.3 years, subjects with HCV genotype 1 and those with multiple HCV genotypes experienced more rapid immunological progression to a CD4 count ≤200 cells/mm^3 compared with genotype 3 patients (adjusted hazard ratio 2.02, 95 percent CI 1.04-3.92 for genotype 1; hazard ratio 2.74, 95 percent CI 0.95-7.90 for multiple genotypes). When the analysis was limited to pre-HAART data, the differences were even greater (hazard ratio 3.92, 95 percent CI 1.51-10.20 for genotype 1; hazard ratio 4.38, 95 percent CI 1.04-18.40 for multiple genotypes).

After further parsing of data from the entire study period, the researchers determined that the increased risk of immunological decline was linked to infection with HCV genotype 1a, but not 1b. Moreover, subjects with only genotype 4—which the researchers identified as being "on the rise among injecting drug users"—experienced significantly slower immunological progression than those with only genotype 1.

Overall, patients with multiple HCV genotypes also experienced faster clinical progression to AIDS or pre-AIDS death (excluding non-natural causes such as overdose, suicide, or accidents), but this did not reach statistical significance (hazard ratio 3.36, 95 percent CI 0.82-13.79). Looking only at data from the pre-HAART era, however, subjects infected with more than one genotype had a significantly higher risk of clinical progression than those with only genotype 3 (hazard ratio 6.54, 95 percent CI 1.39-30.76). Unlike immunological decline, infection with genotype 1 alone was not associated with more rapid clinical progression, and no significant differences in clinical progression were observed when comparing subjects with only genotype 1, 3, or 4.

The authors concluded that HIV disease progression differs by HCV genotype, "being especially enhanced in those [harboring] HCV infection involving more than one HCV genotype." Given that the difference was much greater before the advent of HAART, they suggested that efficacious combination antiretroviral therapy "may diminish the effect of HCV genotype on HIV disease progression."

In their discussion, the authors noted that it is not yet known how multiple HCV genotypes might cause faster HIV disease progression, although other researchers have suggested that different genotypes many interact differently with HIV, or may have differing effects on CD4 cell proliferation within the liver. Since HCV may be cleared naturally by the immune system or eradicated with treatment, and since prior infection with one HCV strain does not prevent subsequent re-infection, the authors recommended that "HCV genotype should ideally be measured prior to HIV infection and longitudinally at different time-points within HIV-infected individuals to gain a better understanding of the effect of HCV genotype on HIV progression." ∎

References

1. Van Asten L, Prins M. Infection with concurrent multiple hepatitis C virus genotypes is associated with faster HIV disease progression. *AIDS* 2004;18:2313-2318.

Olubukunola Jeminusi

For more than three years the *IAPAC Monthly* has featured members of the International Association of Physicians in AIDS Care (IAPAC) who are asked to bare their souls by answering a series of questions similar in nature to those asked in the famous *Proust Questionnaire*.

This month, *IAPAC Monthly* is proud to feature Olubukunola Jeminusi, who is Director of the Sagamu Community Centre, a nongovernmental organization in southwest Nigeria.

What proverb, colloquial expression, or quote best describes how you view the world and yourself in it?
"Love your neighbor as yourself," and "Live and let live."

What activities, avocations, or hobbies interest you?
Teaching, pastoral work, and reading. Future studies and eschatology. I seem to have a knack for fishing out the uncanny.

If you could live anywhere in the world, where would it be?
The Cayman Islands.

Who are your mentors or real life heroes?
Nelson Mandela.

With what historical figure do you most identify?
Jesus Christ.

Who are your favorite authors, painters, and/or composers?
Paul, the Apostle; Alvin Toffler; Leonardo da Vinci; Handel.

If you could have chosen to live during any time period in human history, which would it be?
New Testament times (first century in the Holy Land).

If you did not have the option of becoming a physician, what would you have likely become, given the opportunity?
A pharmacist or parasitologist.

In your opinion, what are the greatest achievements and failures of humanity?
Achievements: Scientific and technological advancements of medicine. Failures: Man's inhumanity to man.

What is your prediction as to the future of our planet one full decade from present day?
A New World Order of humans and humanoids. A new race of masters and slaves. A mad planet awaiting a Messiah, when fiction becomes fact. ∎

Makgatho Mandela
(1951-2005)

Photo: AP/Wide World Photos.

"I announce that my son has died of AIDS. Let us give publicity to HIV/AIDS and not hide it, because the only way to make it appear like a normal illness like [tuberculosis], like cancer, is always to come out and to say somebody has died because of HIV/AIDS. And people will stop regarding it as something extraordinary."

Nobel Peace Prize laureate Nelson R. Mandela announcing the death of his only surviving son, Makgatho Mandela, of AIDS-related complications January 6, 2005. Although he officially retired from public life in 2004, the 86-year-old former South African leader—and one of Africa's most committed campaigners in the battle against AIDS—has kept a busy schedule promoting his various causes, chief among them the fight against South Africa's devastating AIDS epidemic. His 54-year-old son was a lawyer with a background in insurance who kept a relatively low profile. He had been married twice and had three sons, all of whom appeared with their grandfather as he announced the cause of their father's death.

WHY DOES ROSIE PEREZ
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