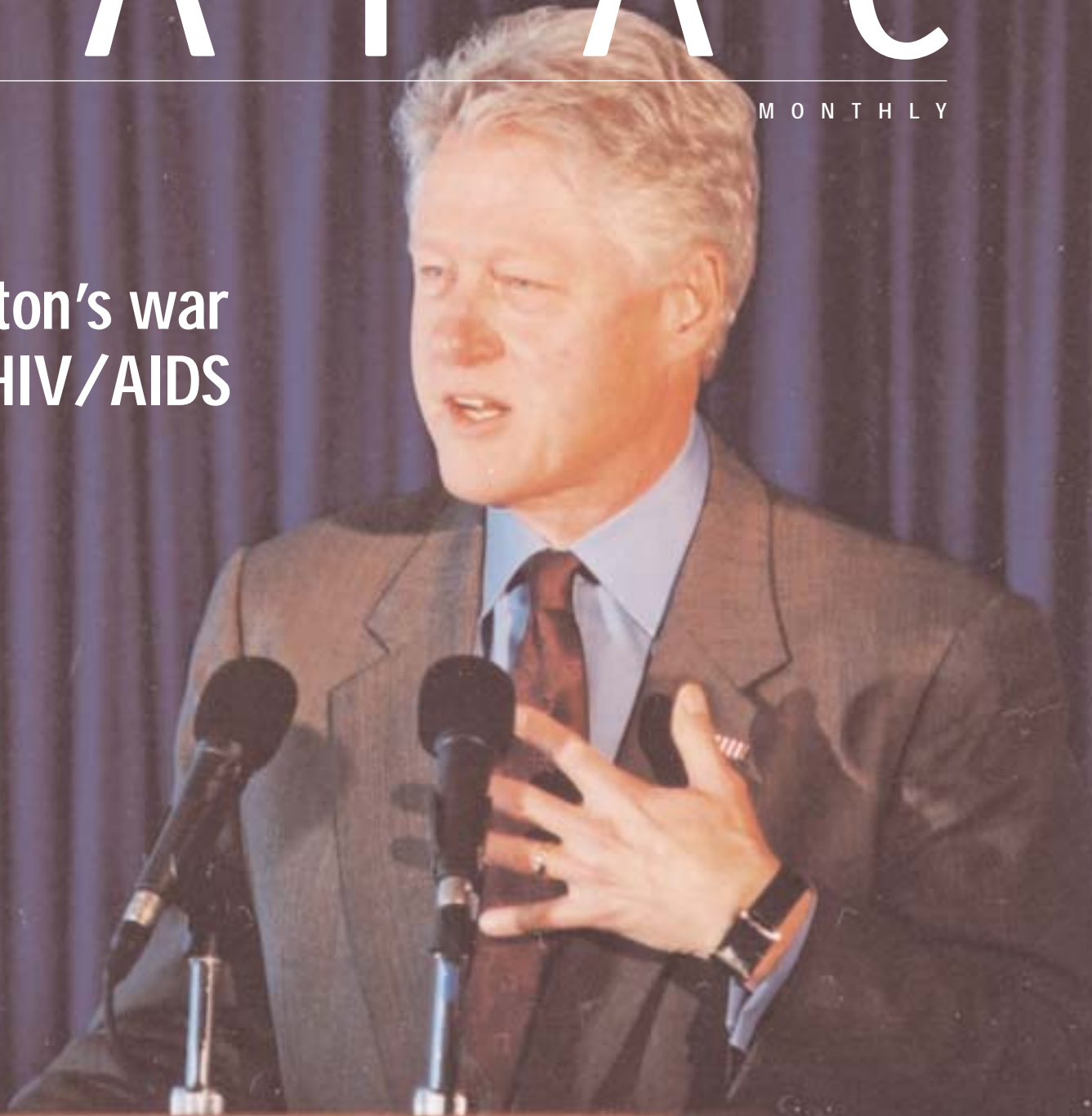


January 2002 VOL. 8, NO. 1

# IAPAC

MONTHLY

## Clinton's war on HIV/AIDS



IAPAC

8

COVER STORY

Clinton's war on HIV/AIDS

Speech delivered by former US President William Jefferson Clinton

During a December 8, 2001, luncheon at which he received IAPAC's 2001 Dag Hammarskjöld Award, former US President William Jefferson Clinton called on governments, businesses, and individuals to do more to fight HIV/AIDS. Estimates of 100 million AIDS cases by 2005, he warned, could become a reality unless more is done to combat the AIDS epidemic.



**INTERNATIONAL ASSOCIATION OF PHYSICIANS IN AIDS CARE**  
**Headquarters Office**  
 Chicago, Illinois, USA

---

**PRESIDENT/CEO** José M. Zuniga  
**SR VICE PRESIDENT/COO** Michael S. Glass  
**VICE PRESIDENT/CMO** Gregory A. Thompson  
**CONTROLLER** Harry J. Snyder

**INTERNATIONAL ASSOCIATION OF PHYSICIANS IN AIDS CARE**  
**Southern Africa Regional Office**  
 Johannesburg, South Africa

---

**EXECUTIVE DIRECTOR** Shaun Conway  
**DEPUTY DIRECTOR** Mulamba Diese

**IAPAC MONTHLY**

**EDITOR-IN-CHIEF** José M. Zuniga  
**MANAGING EDITOR** Lisa McKamy  
**MEDICAL EDITOR** Gregory A. Thompson  
**CREATIVE/DESIGN DIRECTOR** Holly J. Emanuelson  
**ADVERTISING/MARKETING DIRECTOR** Lori Gertz  
**WRITER-AT-LARGE** Mark Mascolini  
**CONTRIBUTING WRITERS** Lisa Keen, Dave MacDougall, Bob Roehr

*IAPAC Monthly* (ISSN 1081-454X) is published monthly by the International Association of Physicians in AIDS Care. All material published, including editorials and letters, represents the opinions of the authors and does not necessarily reflect the official policy of the International Association of Physicians in AIDS Care, or the institutions with which the authors are affiliated, unless otherwise noted.

*IAPAC Monthly* welcomes responses to the material presented. Letters should be sent to Letters to the Editor, *IAPAC Monthly*, 33 N. LaSalle, Suite 1700, Chicago, IL 60602-2601 USA.

Nonprofit postage paid at Kenosha, Wisconsin, and at additional mailing sites. Address all editorial, business, and production correspondence to *IAPAC Monthly*, 33 N. LaSalle, Suite 1700, Chicago, IL 60602-2601 USA. Those submitting manuscripts, photographs, artwork or other materials to *IAPAC Monthly* for consideration should not send originals unless specifically requested to do so by *IAPAC Monthly* in writing.

To order reprints (minimum order required: 250 copies) or request permission to publish an *IAPAC Monthly* article, please call (312) 795-4991 or e-mail [monthly@iapac.org](mailto:monthly@iapac.org).

*IAPAC Monthly* © 2002, International Association of Physicians in AIDS Care. Reproduction of any part without written permission is prohibited. The information contained in *IAPAC Monthly* shall not, in whole or in part, be redistributed, reproduced, or entered into a computer without permission.

14

The latest word on lipodystrophy and mitochondrial toxicity

Mark Mascolini



Protease inhibitors wreak speedy havoc on glucose metabolism and so probably ignite the lipodystrophic fuse long before body fat abnormalities appear, several teams reported at the Lipodystrophy Workshop. But, later on, abnormal fat distribution itself also contributes to insulin resistance. Ultimately, both mechanisms could have cardioconsequences.

DEPARTMENTS

REPORT FROM THE PRESIDENT

5

SAY ANYTHING

34

Cover photograph: Steve Shay, © 2001

## 'Focus on our human bond'

*Editor's Note: The following speech was delivered December 8, 2001, by José M. Zuniga, President of the International Association of Physicians in AIDS Care (IAPAC), at an association-hosted luncheon at which former US President William Jefferson Clinton received IAPAC's 2001 Dag Hammarskjöld Award. The luncheon was attended by, among other dignitaries, former US Secretary of Commerce William M. Daley.*

**M**r. President, Mr. Secretary, esteemed colleagues, distinguished guests:

We are gathered here this afternoon, during a most turbulent of times for our nation and for much of the world, to pay tribute to a national and global statesman—former President William Jefferson Clinton.

Our recent collective experience has enabled us to see with greater clarity all for which we should be thankful, as well as everything toward which we must still endeavor. In the light of what these past months have taught us, we come together to pay tribute and to express our gratitude to President Clinton for his leadership in advancing the issue of HIV/AIDS to the forefront of American public policy and international attention. We do so now both in full cognizance of what such public service means, and with renewed conviction to defend our humanity as we have been reminded of both its delicate nature and how much it truly is a shared and mutual phenomenon.

As we direct our attention to the challenge of stemming the AIDS pandemic, our most crucial task is to remain focused on our human bond, and to let this bond guide our actions across geographic, cul-



Former US President William Jefferson Clinton and IAPAC President José M. Zuniga.

tural, ethnic, and political boundaries. We cannot afford to waiver in our appreciation of the shared worldwide burden that is HIV/AIDS. Yet, this responsibility for the health of every human being, though he or she may often be an ocean away, is not mutually exclusive of *our* desire to provide for our own health, well-being, and security.

For example, despite a continuing decrease in the number of new HIV infections in the United States—achieved in large measure thanks to the Clinton Administration's efforts—we must remember that we remain inextricably bound, each to the other, in this global society in

which diseases discriminate against no one and recognize no boundaries. If a single one of us is in danger, we are all threatened.

Bearing in mind our shared risk and responsibility, if we pan our gaze across the vast landscape of this globe, we see a world that is reeling from the toll that AIDS is taking on humanity. As of December 2001, 40 million children and adults throughout the world are living with HIV disease. This represents an increase of 4 million from last year this time. In Africa, the Caribbean, Latin America, and Asia, the regions most severely affected by the AIDS pandemic, most of the available statistics are especially grave.

Across Africa, for instance, there were 3.4 million new HIV infections in 2001, meaning that of the 40 million people in the world living with HIV, 28.1 million live on the African continent. Further, in several areas of sub-Saharan Africa, 30 percent of pregnant women are HIV positive. Overall, AIDS killed 2.8 million Africans this year alone.

The situation is no better in China, which recently discovered its AIDS epidemic. In Eastern Europe, the number of new HIV infections is rising faster than anywhere else in the world. In the Caribbean, the AIDS epidemic is reaching staggering proportions. Our neighboring countries to the South now have the second highest HIV incidence in the world after sub-Saharan Africa.

It is too easy to view HIV disease as a purely clinical condition, requiring specifically clinical interventions. We must recognize that AIDS is a public health issue which is fed by and which in turn exacerbates parallel epidemics of poverty and social isolation. To point out one of the most poignant examples of this vicious cycle, the hardest hit countries of sub-Saharan Africa could lose more than 20 percent of their gross domestic product (GDP) by 2020 as a result of AIDS. If we carefully examine this gradual crippling of the state, we observe that education, civil administration, health service, and agriculture systems—to name a few of the essential pillars upon which a productive nation is dependent—are being left in ruin.

Near the end of his administration, President Clinton declared AIDS a threat to international security, and led efforts for the United States and its G-8 partner nations to scale up AIDS initiatives. President Clinton did so because he recognized that unless we address AIDS in a comprehensive manner and with due respect for the needs of individual countries and populations, we will fail in our desire to achieve the positive changes to which we have committed ourselves.

The task of combating the social and economic devastation wrought by AIDS is nothing less than a quest for the development of our communities, certainly within our own nation, but with special emphasis on communities in resource-poor countries. This is not to suggest an agenda of community welfare, but rather a process of social change by which the quality of life and the productive capacity of individuals

and their communities are enhanced.

At the center of this process must exist a transformation whereby both the individual and the community are liberated from damaging constraints, and where we strengthen freedom of choice and sufficiency and ensure full participation in social and political processes. In more tangible terms, this means heightened access to employment, living wages, education, healthcare, and social security.

The future productivity of local, national, and regional economies will be determined by the capacity built and fostered at these levels. The very wonders and marvels that history has taught us to expect from our humanity will hinge upon our collective ability to be entrepreneurial, innovative, and most importantly, *healthy*.

Along this path toward health for all, we must strive to operate in an environment informed by the realities faced by our global constituents. We must appreciate, for example, that the range of poverty both within and across boundaries varies greatly, from the HIV-infected Nigerian mother of three who is so poor that she and her young family barely manage to sustain life, to the HIV-infected Indian rickshaw driver who remains poor more so by virtue of the lack of socioeconomic opportunities that might otherwise enable him and his family to achieve the quality of life common to the average individual and his/her family in the industrialized world.

The challenges posed by the AIDS pandemic in these countries, as well as their solutions, must therefore be tailored to accommodate the realities and need of these particular populations. Just as there is no panacea, there can be no one solution or intervention that is universally transferable and applicable. And, there can be no solution or intervention for HIV/AIDS that does not take into account the growing chasm between rich and poor, privileged and underprivileged. We must hasten to redress this gravest problem, for if the poor are left hopeless, poverty will corrode the fabric of our societies through confrontation, violence, and civil disorder. Far too often, those who are poor are also sick and disabled, whose lost social and economic productivity and whose strain on what minimal social services there are further threaten to dissolve that social fabric.

In our commitment to attack the AIDS

pandemic, we must also re-orient the nature of the dialogue that currently exists between those in the North and those in the South. During the last decade, we learned that it is not enough to simply increase the size of the pie; the way in which it is shared is deeply relevant. Those of us in leadership positions must work to ensure that the myriad voices of those in developing world countries—those who bear the greatest burden of HIV disease—are heard. We have seen that in the face of overwhelming odds, and despite obstacles they must surmount, even the most deeply affected of countries can begin to turn the tides of circumstance.

Uganda, for example, responded to its AIDS crisis with remarkable determination and success. Through public and private efforts, Uganda's HIV infection rate was reduced from 14 percent in the early 1980s to below 8 percent today. Without diminishing the many contributions of the global community, this triumphant change must be appreciated and respected foremost as the successful development of Uganda by Ugandans. This is a story that all developing world countries are equally capable of achieving if their participation as equal partners is carefully fostered.

In the 20th year of this global pandemic, there is also an unmistakable need to accelerate the pace of our interventions:

- We must scale up voluntary counseling and testing programs and increase prevention interventions conducted in collaboration with affected communities.
- We must find creative and coordinated ways to expand access to inexpensive medications which can reduce HIV-associated morbidity and mortality.
- We must improve national blood supplies, strengthen laboratory capacities, and build greater and more appropriate medical and social support infrastructure.
- And, while we enhance those interventions already known to us, we must remain focused in our efforts to discover and deliver a vaccine or vaccines to prevent HIV infection and/or cure HIV disease.

I am convinced that the International Association of Physicians in AIDS Care and our membership—with political and other support—are uniquely placed to facilitate and drive this process by battling complacency and advancing commitments that will make a difference in the lives of countless people living with and at risk for HIV/AIDS.

That so many of us are here this afternoon is a testament to our shared individual and collective resolve to battle the complacency and advance the commitment to which I have alluded. To quote former UN Secretary-General Dag Hammarskjöld, the man after whom is named the award President Clinton is to receive today, “to let oneself be bound by a duty from the moment you see it approaching is part of the integrity that alone justifies responsibility.” Duty. Integrity. Responsibility. These three hallmarks stand as beacons of the truly democratic spirit to which we must look for guidance in meeting our mutual obligation to the millions of men, women, and children throughout the world—but especially on the African continent—who are dehumanized by circumstance and disease.

When we acknowledge our responsibilities and are compelled and determined to provide for the health of all, let us agree to proceed with both urgency and compassion. Let us look to and uphold in our thoughts a day when AIDS will be no more. Let each of us take pride and joy in our ability, through acts both small and great, to effect changes along the chain of being which may mean the difference between life and death for others. Because, as British Prime Minister Tony Blair recently reminded us, “The test of any decent society is not the contentment of the wealthy and strong, but the commitment to the poor and weak.”

Holding fast to this spirit of collective responsibility and commitment, I reach out to those of you here this afternoon, along with your respective colleagues and constituents, and look forward with enthusiasm to our many partnerships. After all, our partnerships and subsequent actions will speak louder than words as we work to remedy the greatest public health challenges of our time.

I thank you for your presence here and your attention to the important contributions made by President Clinton. And, I thank you on behalf of IAPAC’s 10,800 members in 83 countries for your commitment to a more global engagement in the now 20-year-old battle against HIV/AIDS.

Thank you. ■

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

## IAPAC set to open Paris office in 2002



battling complacency  
advancing commitment

The International Association of Physicians in AIDS Care (IAPAC) announced December 18, 2001, plans to open a regional office this year in Paris. The announcement followed a unanimous vote by the IAPAC Board of Trustees during its December 17, 2001, meeting in Chicago, to formally establish a presence in a geographic region that represents the second highest concentration of IAPAC members.

In July 2000, IAPAC opened its IAPAC Southern Africa Regional Office (IAPAC-SARO) in Johannesburg, South Africa. IAPAC-SARO’s mission is to build infrastructure, develop capacity, and implement targeted programs that enable physicians and other healthcare professionals throughout the region to provide appropriate, comprehensive care and support for local HIV-infected populations. In 2002, IAPAC-SARO is coordinating many such programs, including I-Med Exchange and Right-to-Care.

“The need for IAPAC to actively participate in the European region is made even more relevant by the host of opportunities for developing and coordinating programs in Western and Eastern Europe through which IAPAC may have a measurable impact on HIV care in the region,” said Allen I. Freehling, Chair of the IAPAC Board of Trustees.

IAPAC President/CEO José M. Zuniga explained that, unlike Southern Africa, Western Europe counts on a large group of dedicated and informed physicians who are actively engaged in meeting the clinical and social challenges of HIV/AIDS in their respective countries. However, there is a great deal of supple-

mental educational and advocacy support Western European physicians require.

“And, of note, similar to the situation faced in the Southern African region, it could be argued that there are few equivalent places than Eastern Europe where the IAPAC credo ‘battling complacency, advancing commitment’ is as relevant,” Zuniga said.

IAPAC plans to open its IAPAC European Regional Office (IAPAC-EURO) in July 2002. In the meantime, IAPAC will collaboratively advance publications, Web-based media, and clinical symposia initiatives with the European AIDS Clinical Society (EACS). Zuniga and EACS President Christine Katlama signed a Letter of Agreement in November 2001 laying out a framework for collaboration between the two institutions.

The IAPAC Board of Trustees also endorsed the creation of an IAPAC North America Regional Office (IAPAC-NARO) to exclusively implement medical education and advocacy initiatives as well as coordinate membership services in Canada, Mexico, and the United States—all of which had previously been handled through IAPAC Headquarters (IAPAC-HQ) in Chicago. An announcement will be made within the next two months regarding IAPAC-NARO’s physical location as well as the appointment of its Executive Director.

In other news, IAPAC’s Board of Trustees approved a multi-region workplan and budget of US\$4.3 million for IAPAC’s operations in 2002, to include publication of a Southern African *IAPAC Monthly* edition commencing in March 2002.

# Clinton's war on HIV/AIDS



Former US President William Jefferson Clinton accepts the 2001 Dag Hammarskjöld Award from IAPAC President José M. Zuniga. The former president urged governments, businesses, and individuals to redouble their efforts to combat the AIDS epidemic lest predictions of 100 million potential AIDS cases by 2005 come true.



Photo: Nannette Beckway, © 2001

**T**hank you very much... Ladies and gentlemen, I thank you all for being here to support this cause...

I am delighted to be here and to receive an award named for Dag Hammarskjöld. When I was a boy, he was my first United Nations Secretary-General. He was a magnificent man. He wrote a set of autobiographical sketches and insights called "Markings," that bore a remarkable resemblance to the meditations of Marcus Aurelius, written in the 2nd century AD. And when I read these Markings, they had a huge impact on me and how I thought about the nobility of public service and how people should live. And when my daughter was finishing Stanford [University], and she is in general far better read than I am, but I learned that she had never read it. So I gave her a copy of Dag Hammarskjöld's book written so long ago. So I am grateful for this [award].

But most importantly, I am here because I support the work of the International Association of Physicians in AIDS Care—physicians working on behalf of people

---

*Editor's Note: This speech was delivered December 8, 2001, by former US President William Jefferson Clinton at an International Association of Physicians in AIDS Care (IAPAC) luncheon at which he received the association's 2001 Dag Hammarskjöld Award for his leadership on HIV/AIDS throughout his eight-year presidency.*

living with HIV and AIDS around the world. For me, this is personal and political. I'll never forget when I was at the hospital bed of the first friend I had to die of AIDS. The last friend I had to die of AIDS died last month. And then I'll never forget the first time I went to Africa as President, and realized that in South Africa, roughly 30 percent of the adult population was HIV positive; or the first time I saw an African leader in Nigeria, President [Olusegun] Obasanjo, openly and publicly embrace a woman and her husband who were both HIV positive, to try to drive the sense of denial out of the country that has kept so many countries from adopting adequate prevention policies. So for me, this is both personal and political in the finest sense.

I want to talk a little bit about what I think our government and governments should do, and what the United Nations is trying to do under the leadership of Kofi Annan, who is a worthy successor to Dag Hammarskjöld, and who won the Nobel Peace Prize this year, and richly deserved it was. But I also want to say that we cannot deal with this problem successfully without the support of people like you, and doctors like the doctors in this association.

So let me try to explain, if I might, why it's a good thing you're here, and why supporting the President [George W. Bush] and our allies in the fight in Afghanistan and in building effective domestic defenses

against terrorism at home is really part of the same mission as supporting what these doctors are doing. If you look at what happened on September 11th, and if you look at the global AIDS epidemic, they both show that we live in a world without walls, an age of interdependence, where borders simply don't stop much, good or bad, anymore. Unless you want to rebuild those walls, which I doubt we could do anyway, you have to try to build a world in which we have more partners and fewer terrorists, and a world in which problems half a world away are stopped not only for humanitarian reasons, but before they come back to us.

We have spent 20 years in this country trying to get a hold of the AIDS epidemic. We got our infection rate down to under one percent of the adult population. But there are some discrete populations in America where the rates are going up again. There are some rural areas in the South that are remarkably, from a socioeconomic point of view, like some of the places we work in Latin America in Africa, where the rates are going up again. The second fastest growing AIDS rate in the world is in the Caribbean, just down on our front door. I've been in a clinic in the Dominican Republic to see what they're doing there. And, you know, Hillary [Rodham Clinton] represents New York in the [US] Senate, that we have a million Dominicans in

New York. Do you really believe that we can keep the American rate down if our nearest neighbors have the second fastest growing rate in the world?

So this is a very serious part of our future. I go all around the country now talking to young people. And we have these huge crowds at college campuses because they never lived through anything like what we're going through now. You know, the Cold War was over in 1989 before most of them started thinking about politics. And it was effectively over before then. And they had no experience with Vietnam. They don't have parents who talked to them about Korea and World War II. And, unlike me, they never had any school drills where they had to go get in a fallout shelter because we're preparing for a nuclear bomb to fall on us. So all of a sudden here they are, after 10 years or so of positive experiences and sort of relative security, feeling uncertain.

We have gotten enormous benefits, enormous, out of this world without walls. It's given us an enormous part of our jobs. It's brought immigrants from all over the world to this country and into this room and made America a much more interesting, rich, diverse place. It has enabled us to do great things as a people. It's driven income up and poverty down, [and] allowed us to cut the welfare rolls in half. It made America a better place. But it made us more vulnerable. You can't take the walls down and claim all the benefits and say "I just hope the problems will never appear." And there are lots of people who worked for years and years and years, career people, hoping against hope that a day like September 11th would never come.

But the larger point I want to make is that the AIDS pandemic and the fight against terrorism should be seen by you as a part of your obligation as a citizen of this country and a citizen of the world to claim the benefits and roll back the burdens of a world without walls. So we should support the President and our allies in the fight in Afghanistan. We should support the priority of constructing the most effective possible defense here at home. You should believe that, as I tell people all the time, no terrorist campaign in history has ever succeeded and this one won't either. There may be more victims and it may be some time gap before we do it, but we will prevail here.

But if you want the world I believe we

want for our children and our grandchildren, then it's not enough just to support the campaign in Afghanistan and to build a defense. I mean, we don't want to build a future where everybody who makes a good living lives behind a wall and where the world becomes more divided in different ways. So if you don't, then we have to spread the benefits and reduce the burdens of the 21st century world and to go back to something that was said earlier, we have to develop a global philosophy that what we have in common is more important than our differences. And the only thing we really have in common is our humanity.

Now, that's what this whole fight against AIDS is all about. You heard the statistics earlier, but I want to repeat a couple of them. There are now 40 million people living with HIV and AIDS in the world. Twenty-five million people have had it and have perished. There are about 14,000 new infections every day. More than half of the new infections are among people between the ages of 14 and 24. If we don't do something to turn this around by the year 2005, instead of 40 million AIDS cases there will be 100 million AIDS cases. When we have World AIDS Day in December 2005, some somber person will stand up and we will all be shocked to find out that we've got 100 million AIDS cases.

... That's exactly what's going to happen unless we turn it around. And there cannot be 100 million AIDS cases in the world without severe, adverse, direct consequences to the United States, to Illinois, to Chicago. You have to understand that. What will they be? Assuming, first of all, since the second fastest growing rate of AIDS is on our front door in the Caribbean, more Americans will become HIV positive. They'll give it to other Americans and it will run your healthcare bills up and people you know will die. Children will have their futures cut off. That's the first thing.

[The] second thing is, how many countries do you think we can stand in Africa and Latin America and other places that have infection rates right at 30 percent? If you go from 40 million to 100 million AIDS cases, and the growth is in the areas where the growth is greatest now, I promise you some of these fledgling democracies will fail. There will be more wars and more violence. And you'll have all these young guys out there thinking, "Well, why shouldn't I get a machine gun and go shoot somebody? I'm not going to

live more than another year anyway." A phenomenon we have already seen in tribal wars in Africa, in my time.

The third fastest growing rate of AIDS is in India, where they've got about 10 million AIDS cases and a billion people, the largest democracy in the world, but where I see so much and hear so much like I heard in Africa five years ago, where people are kind of resisting getting into the whole business of prevention, because for a lot of cultures, they're shy and culturally conservative. And they don't know how to go talk to people about how you get AIDS. But the longer we wait, the more people are going to die.

The biggest country in the world, China, just acknowledged they have literally twice as many AIDS cases as they had previously thought. And only four percent, four, f-o-u-r percent of the adult population even know how it's contracted and spread. China is trying to get in the World Trade Organization and, you know, we're trying to make all kinds of agreements so we have a peaceful future with them. The Chinese are going to be lifted out of poverty. The Indians have a chance to be lifted out of poverty. They're making half of all the software in the world in India now. And they're facing these kind of problems. We cannot expect America not to be affected by this. This is a recipe not only for human misery, explosive healthcare costs, but for more war, more instability and more political problems for America.

Now, the good news is none of this has to happen. Uganda, with no medicine, cut the [AIDS-related] death rate in half in five years. You heard that earlier. Just prevention. Brazil, with prevention and medicine, cut the death rate in half in three years, their hospitalization rate by 80 percent in three years. We can do this. But we have to recognize what we're up against. The fastest growing rates of AIDS are no longer in Africa, where 70 percent of the cases exist. The fastest growing rates of AIDS are in the former Soviet Union. So now, in the common fight against terrorism, we have a new alliance with Russia, a new hope that we'll have stability there. What are you going to do if in all those little countries, Russia and the countries along there, all the public health systems break down and AIDS explodes? And all the stability and partnership and peace and opportunity we

hope to give those young people over there, in a way that removes from our children's generation the kinds of threats we grew up with, becomes impossible because they've got infection rates of 30 or 35 percent?

Now, I will say again, it doesn't have to be that way. I have been to Brazil and see what they do. I have been to Uganda. I've seen what they did. I have been in the townships in Soweto and other places in South Africa and seen these clinics. I've been in a little village in rural Nigeria and watched the kids put on a play about AIDS and get over their being self-conscious about talking about this, because they decided they would like to live after all.

It does not have to be this way. We have to have more prevention and more treatment. We have to have more doctors out there. The drug case, the case the drug companies brought against South Africa to try to stop them from putting out generic drugs, was resolved successfully earlier this year. And one of the things I particularly appreciated was that the incoming [Bush] Administration, which had taken a different position a year ago, stuck with our position and told the drug companies we had to give people with HIV in poor countries free or reduced [cost] drugs so they could stay alive. So we resolved the case. Now it's just a question of working out the contracts in all these countries and getting the medicine out there. That's going to happen. So that's good.

We also, however, need more doctors, more nurses, more health clinics, and that's where this group comes in. The efforts of these IAPAC physicians who are working around the world against AIDS with care and with advocacy are critical. And now here's where you come in. So we need the medicine. It's coming. We need the prevention programs. We have models. We need the people in the local areas to get their act together and get out of denial, otherwise there's nothing the rest of us can do. Right? And we need the doctors, the nurses, [and] the clinics.

All right. What else do we need to do? We need to prevent the mother-to-child transmission. We have that. We need effective treatments for the kind of opportunistic infections that come with AIDS. And we need to lobby to continue to develop a vaccine and a cure. All of this is very important. Where do we come in? The Secretary-General of the United

Nations has asked us, as a world, both governments and as citizens, to come up with [US]\$7 to [US]\$10 billion a year for AIDS and the other infectious diseases that together claim one in four of all the people who will perish this year. AIDS, tuberculosis, malaria, and infections related to diarrhea cause one in four of the deaths in the whole world every year.

So Kofi Annan says, for [US]\$7 to [US]\$10 billion, we could make a real dent in this. Let's take the high number, [US]\$10 billion. Our share of that, based on our share of the world's gross domestic product would be about [US]\$2.2 billion. That sounds like a lot of money. That is one-eighth of one percent of the [United States'] federal budget.... one-eighth of one percent of the federal budget. It is a lot of money, but it's also a lot cheaper than going to war. The current conflict in Afghanistan, I read somewhere, I don't know this, but I read somewhere that it costs about [US]\$1 billion a month, which sounds about right because we don't have many troops on the ground there—the Northern Alliance cleared out the Taliban and now we have our Special Forces there who are looking for Mr. [Osama] bin Laden—and because we didn't have to have an enormously heavy bombing campaign, because there weren't all that many strategic targets. So let's assume it's [US]\$1 billion a month. That's five times on an annual basis what it would take us to pay our share of the battle against AIDS, which has already infected 40 million people and killed 25 million. Do you think it's worth it? I do.

And some of it can be given with tax dollars. Some of it can be given as you're giving it here to support these doctors. But the point I want you to understand more than anything else is we've got to do it. We have the money. Do you remember the guy who said, "I rob banks because that's where the money is?" You might wish some other country would help pay for this. But [the United States] is where the money is. And this is where the AIDS problems will be ultimately residing unless we turn this around.

I think about all these people I know who have worked for 20 years to turn the AIDS epidemic around in America. And to think it could come right back into America because we didn't do what it took to keep it out of the Caribbean, out of the former Soviet Union, out of India,

out of all these other places. And we know from Brazil, from Uganda, from Senegal, from all these places, we know that these developing countries can turn it around. It is not inevitable that we'll have 100 million cases. That's what all this is about.

So these doctors, you know, these doctors could be doing something else. They could be out here and making a good living, doing something else. But they're going to go out there and try to save these lives. And the contribution you gave is going to enable them to do it. But when you leave here, I want you to think about what I'm telling you. And I want you to tell your congressmen and your senators that you will support America paying its fair share of the United Nations Secretary-General's [Global AIDS and Health Fund]. That it sounds like a lot of money, but it's a lot cheaper than going to war, and it's a lot cheaper than what we're going to pay if we don't deal with it. It is the morally right thing to do because we live in a world without walls.

Let me just say parenthetically, the same argument applies to our fair share of getting 100 million kids in school that never go to school. Or our fair share of trying to control the chemical and biological and nuclear products around the world that terrorists are trying to steal. We just can't avoid the fact that if we live in a world without walls, we have to be part of dealing with the challenges, spreading the benefits like the economy, and reducing the burdens.

But there is no more urgent thing than dealing with AIDS. I'm telling you, I know, I have been in these places. I know what is going to happen if we have 100 million AIDS cases in five years. It would be the biggest health problem since the plague killed one-quarter of Europe in the 14th century. In 750 years, it would be the biggest health problem. We don't have to put up with this. We can do better. These doctors are giving their lives to do better. So thank you for supporting them. But also support your political leaders, so that America can pay its part of turning this around.

Thank you and God bless you. ■

*William Jefferson Clinton was the 42nd President of the United States, serving from 1992-2000.*



The AIDS Foundation of Chicago (represented here by its Executive Director, Mark Ishaug), Miss Universe 1999 Mpule Kwelagobe, and Lieve Fransen of the European Commission, received IAPAC's 2001 Jonathan Mann Health Human Rights Awards at the Honoring Our Heroes tribute dinner held December 17, 2001, in Chicago.

**A**fter a two-month postponement due to the tragic events of September 11, 2001, the International Association of Physicians in AIDS Care (IAPAC) held its Honoring Our Heroes tribute dinner December 17, 2001, at the Field Museum in Chicago. Lieve Fransen, Head of the European Commission's Unit for Social, Human, and Cultural Development; Mpule Kwelagobe, Miss Universe 1999; and the AIDS Foundation of Chicago received IAPAC's 2001 Jonathan Mann Health Human Rights Awards that evening.

The tribute dinner's host, Allen I. Freehling, Chair of the IAPAC Board of Trustees, recognized IAPAC's 2001 award recipients for their unrelenting work to advance the cause of men, women, and children living with and at risk for HIV disease.

"The work these individuals are

accomplishing exemplifies IAPAC's motto—battling complacency, advancing commitment—and is exactly what must happen at this time of unprecedented need worldwide for renewed focus and energy to battle HIV/AIDS," Freehling told a crowd of 200 IAPAC supporters attending the tribute dinner.

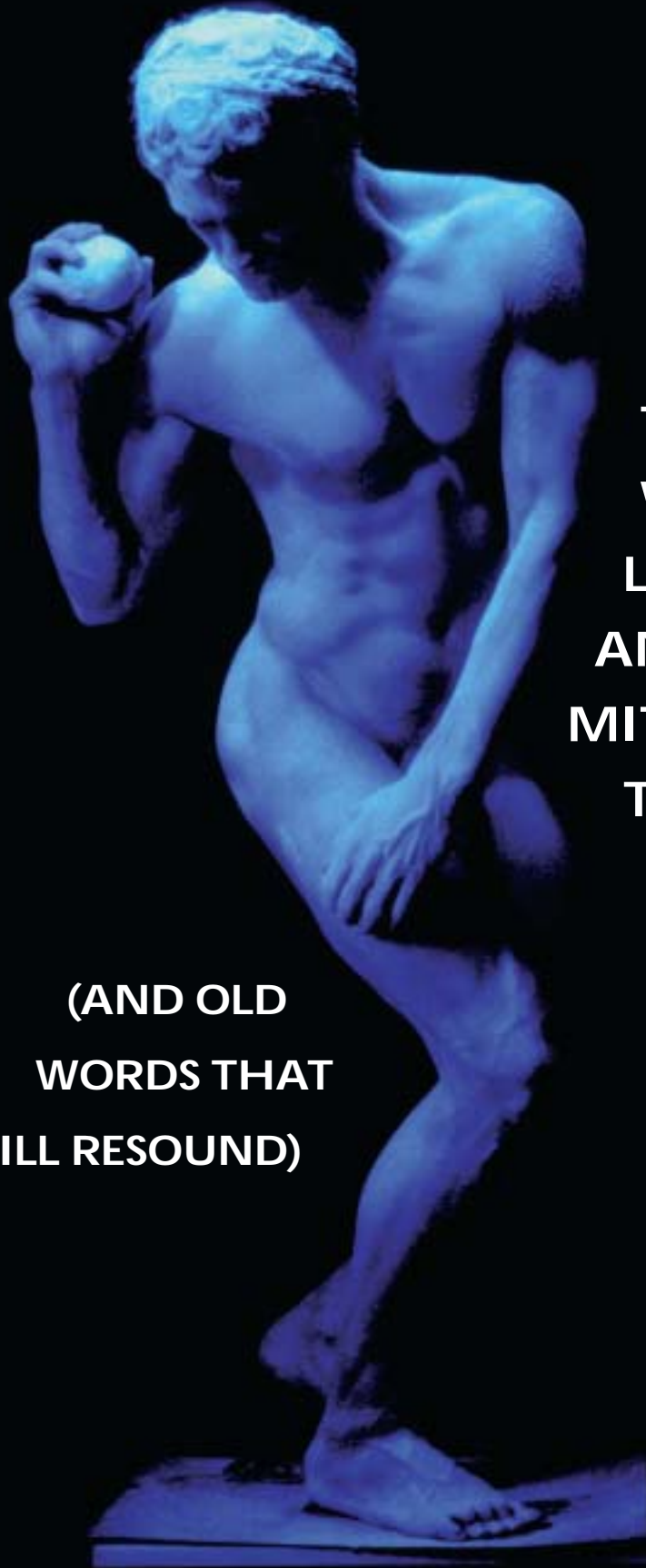
Former US President William Jefferson Clinton, who could not attend the re-scheduled Honoring Our Heroes event because of an engagement in Europe, accepted his 2001 Dag Hammarskjöld Award at a special IAPAC luncheon held December 8, 2001. In his acceptance speech, which was broadcast via video December 17, the former president called for a redoubling of efforts to combat HIV/AIDS.

Also absent from the event because of scheduling conflicts were honorees Sandra Thurman, former Director of the White House Office of National AIDS Policy, and Veronica Moss, Group Medical

Director of Mildmay International. Thurman was the recipient of a fourth Jonathan Mann Health Human Rights Award. Moss was the recipient of IAPAC's 2001 Hero in Medicine Award. Both awards will be hand-delivered to their respective recipients later this year by IAPAC President José M. Zuniga.

In the meantime, Zuniga announced January 7, 2002, the selection of United Nations Secretary-General Kofi Annan to receive IAPAC's 2002 Dag Hammarskjöld Award at the association's fourth annual Honoring Our Heroes tribute dinner. The award will be presented in September 2002 to coincide with the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in San Diego. Zuniga said the event's date and venue would be announced in February 2002.

3 R D I N T E R N A T I O N A L W O R K S H O P O N A D V E R S E D R U G  
R E A C T I O N S A N D L I P O D Y S T R O P H Y I N H I V  
O C T O B E R 2 3 - 2 6 , 2 0 0 1



**THE LATEST  
WORD ON  
LIPODYSTROPHY  
AND  
MITOCHONDRIAL  
TOXICITY**

**(AND OLD  
WORDS THAT  
STILL RESOUND)**

**M**any of the words that matter most in English started out Greek: genesis, stasis; agony, pathos; paradigm, metaphor; icon, iconoclast; comedy, tragedy. And that very short list doesn't even touch the ample lexicon of Greek-derived medical terms: atrophy, hypertrophy, lipodystrophy, mitochondria, osteopenia, to name just five.

You might think the organizers of the 3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV had some subtle linguistic motive in mind when they set the meeting in plain view of the Parthenon and a short stroll from the agora where Socrates asked all those irksome questions. But they didn't. They just figured it would be convenient for attendees who wanted to take in both the Lipodystrophy Workshop and the 8th European Conference on HIV, which followed hard upon.\*

But even the least classically inclined attendee, sitting within shouting distance of stones that echoed Sophocles (and Aristophanes), might see some plot development in this move to Athens. The first and second editions of the Lipodystrophy Workshop made headlines with clinical findings almost Doric in their sturdy simplicity: Yes, nucleoside analog reverse transcriptase inhibitors (NRTIs) figure profoundly in the lipodystrophy syndrome. Yes, high triglycerides and ever-widening waistlines have cardiovascular consequences.

At the third workshop, though, the message had turned decidedly Corinthian in its curlicue complexity. If only our Greek phrase books gave some clue to the roles of PPAR- $\gamma$ ,  $\beta$ -cell insensitivity, and TNF- $\alpha$ 's anti-adipogenic synergies, not to mention the parts played by wholly Roman thespians like GLUT4 and SREBP-1. But not to worry. Most researchers proved ready translators at this meeting. And though the toxic plot has taken on more twists and turns, certain story lines evolved clearly:

\*This article reviews antiretroviral side effect studies from the 3rd Lipodystrophy Workshop and the 8th European Conference on Clinical Aspects and Treatment of HIV Infection, held October 23-26 and 28-31, 2001, in Athens. Abstract numbers from the European meeting are preceded by an O (for oral) or a P (for poster). Other news from the European Conference will be reported in a separate article.

- Protease inhibitors (PIs) wreak speedy havoc on glucose metabolism and so probably ignite the lipodystrophic fuse long before body fat abnormalities appear.
- To remedy metabolic mix-ups, research is turning away from anabolic agents and recombinant human growth hormone and toward insulin-sensitizing and lipid-lowering agents (but early results with these better-targeted therapies are mixed).
- NRTIs' toxic effects on mitochondria assumed more import with new research (but bigger prospective studies are still needed).
- New work continues to implicate stavudine (d4T) and didanosine (ddI) in inflated lactate levels (but the clinical value of lactic acid screening remains uncertain).
- The link between osteopenia and HIV seems stronger than the link between osteopenia and anti-HIV medicines.

If side effects research has begun to get its alphas and betas in order, it remains far from any omega. As noted by one of the workshop's organizers, Kathleen Mulligan (University of California, San Francisco), "For those of you who came to this meeting looking for answers, I'm sorry for your disappointment."



Insulin's odyssey through the body amounts to an epic tale for people with HIV infection, especially those taking protease inhibitors. For insulin, Attica is the pancreas, the home base whence it sallies to liver, muscle, and fat. All three ports figured in the saga that unfolded at the Lipodystrophy Workshop.

The linchpin in this plot—and probably in the evolution of the PI metabolic syndrome—turns out to be insulin resistance. As the Royal Perth Hospital's Simon Mallal and David Nolan explain in a concise review of the workshop,<sup>1</sup> insulin resistance is "an impaired metabolic response to the presence of insulin." When the gods are smiling, insulin orchestrates a complex metabolic symphony after eating. It spurs the uptake of glucose—or "metabolic fuel," as Mallal and Nolan put it—by muscle, a process that depends heavily on an insulin-driven glucose transporter called GLUT4. Insulin also promotes storage of glucose, as glycogen, in muscle and liver. And it

regulates glucose and lipid metabolism in adipose tissue—fat. On top of all that, insulin shuts off the slow drip of fatty acids from adipocytes into the circulation, a process called lipolysis, until glucose stores run low in the fasted state.

Little wonder, then, that insulin resistance stirs a pot of trouble. The Lipodystrophy Workshop succeeded, as few forums do, in twining together several strands of insulin resistance research into a coherent etiologic thread, though loose ends certainly remain. Two things appear to be happening, explained Steven Grinspoon (Massachusetts General Hospital, Boston) in a postworkshop interview:

"The first is that the protease inhibitors probably have some direct effect to mediate insulin resistance." Studies in cells and animals—including humans—now show that protease inhibitors promote insulin resistance and inhibit glucose transport. And they do so very quickly. Second, Grinspoon added, "there's an emerging recognition that abnormal fat distribution per se also contributes to insulin resistance," possibly by increasing lipolysis, dumping fat into the circulation.

These mechanisms may be independent, but they work together in people who take PIs for a while, a Scylla and Charybdis teamed to wreck insulin-mediated metabolic equilibrium. Here's the evidence workshop attendees heard:

### An immediate insult on insulin

At last year's Lipodystrophy Workshop, Mustafa Noor (University of California, San Francisco) showed that four weeks of standard-dose indinavir significantly increased fasting plasma glucose, insulin, and insulin resistance in 10 HIV-negative volunteers.<sup>2</sup> In a return appearance this year, he showed that a single 1,200-mg dose of indinavir speedily bred insulin resistance in six healthy men [abstract 3]. Insulin sensitivity slipped by an average 34 percent in this double-blind, placebo-controlled, crossover study, cutting insulin-stimulated glucose disposal from 14.1 to 9.2 mg/kg/minute ( $P < 0.001$ ).

How could a protease drug gum up glucose disposal so quickly? Noor proposed that his findings reflect a mechanism described a year ago by Haruhiko Murata (Washington University, St. Louis). Murata traced the problem to direct impairment of glucose transport in *Xenopus* oocytes, where 100  $\mu$ M of indinavir inhibited

activity of the GLUT4 glucose transporter by 45 percent.<sup>3</sup>

And the Washington University team turned up in Athens with more evidence implicating PIs in gridlocked glucose traffic. This time Murata showed that indinavir inhibits glucose uptake in a dose-dependent manner in primary rat fat cells, by 15.6 percent at 1  $\mu\text{M}$ , by 34.6 percent at 5  $\mu\text{M}$ , and by 51.5 percent at 10  $\mu\text{M}$  [abstract 1]. These indinavir concentrations, he noted, lie “well within the physiological range” that indinavir achieves in humans (<10  $\mu\text{M}$ ). Looking again at the PI’s effect on glucose transporters, he confirmed selective inhibition of GLUT4, “believed to be the principal transporter isoform mediating insulin-stimulated glucose uptake” in fat as well as in skeletal and cardiac muscle.<sup>3</sup> In the published study, Murata showed that ritonavir and amprenavir similarly inhibited GLUT4.

Murata’s colleague Paul Hruz pursued this line of inquiry not in rat cells, but in whole rats [abstract 2]. Using the gold-standard test for insulin resistance, the euglycemic hyperinsulinemic clamp, he found that the glucose infusion rate needed to maintain a healthy glucose level fell 16 percent with 14  $\mu\text{M}$  of indinavir and 48 percent with 27  $\mu\text{M}$  of indinavir. Although those drug concentrations exceed levels reached in humans, indinavir’s half-life is much shorter in rats than in humans. When Hruz stopped the indinavir infusion, insulin sensitivity climbed back toward normal within four hours.

Although stopping the drug reversed this “initial insult” to insulin sensitivity, Hruz added, the same quick turnaround may not be seen with secondary mechanisms of insulin resistance, like those caused by obesity. He suggested that this immediate effect may result from direct binding of protease inhibitors to GLUT4, but that remains a hypothesis.

A small study in humans—six men with DEXA-confirmed lipodystrophy while taking indinavir/ritonavir or saquinavir/ritonavir—suggested that muscle, not fat, is the “primary site” of insulin resistance in people taking protease inhibitors [abstract 4]. Comparing the PI-treated men with six treatment-naive seropositive men, Georg Behrens (Hannover Medical School, Germany) charted significantly lower whole-body glucose disposal in the PI takers (1.47 versus 4.07 mg/kg/min,  $P = 0.025$ ). Using a three-compartment model, he calculated that 48 percent of whole-body

glucose disposal could be traced to skeletal muscle in the men taking PIs.

Behrens used radiolabeled PET scans to stalk glucose in muscle, but another method—sugar transport in L6 microtubules—failed to confirm the role of impaired GLUT4 transport by indinavir, saquinavir, or ritonavir, while suggesting that insulin signaling may be more sensitive to PIs in adipose tissue than in muscle [abstract 48]. Simon Mallal and David Nolan assure us that L6 microtubules are a “widely used” *in vitro* method to assess insulin signaling in muscle.<sup>1</sup> They also suggest that the L6 microtubule results presented by Ralph Germinario (McGill University, Montreal) may not be “at odds” with Behrens’ findings, “as it has been demonstrated in an animal model that an adipose-specific GLUT4 defect can induce insulin resistance in muscle as well as liver.”

Still, Germinario’s findings raise the clear caution that pasting together results gathered by different assays in cells, animals, or humans will not always yield a coherent picture. In summarizing some of this work at the end of the meeting, Kathleen Mulligan stressed that Behrens’ results don’t mesh cleanly with the GLUT4 findings of other investigators. Behrens pinpointed not only a defect in glucose transport into cells, but also a problem with glucose phosphorylation. Whereas glucose transport is mediated by GLUT4, she noted, glucose phosphorylation is not.

“We shouldn’t assume,” Mulligan concluded, “that a nice series of studies on one mechanism [GLUT4] rules out other mechanisms.”

### Fat’s long-term fallout

Michael Dubé (Indiana University, Indianapolis) hoisted another cautionary flag in reviewing the studies of Noor, Murata, and Hruz. Although their work convincingly showed that PIs start fouling up glucose flux within hours, that doesn’t mean this immediate effect is more important than the long-term fallout of fat buildup on insulin resistance.

Dubé’s point had already been made in a case-control study of 19 antiretroviral-treated men with lipodystrophy (11 of them taking PIs) and 8 healthy controls matched for age and body mass index [abstract 7]. The men with lipodystrophy had a higher waist-to-hip ratio than the controls and a higher ratio of visceral adipose tissue to total adipose tissue. Steven Grinspoon and

colleagues hypothesized that increased lipolysis (fatty acid release from adipocytes) and the resulting surge in circulating fatty acids contribute to insulin resistance in people with HIV lipodystrophy.

Rates of lipolysis proved significantly higher in the lipodystrophy group than in the controls after an overnight fast (4.1 versus 3.2  $\mu\text{mol/kg/min}$ ,  $P = 0.02$ ) and after oral glucose challenge (4.8 versus 3.5  $\mu\text{mol/kg/min}$ ,  $P = 0.02$ ). After the challenge, free fatty acids climbed in the men with lipodystrophy; levels correlated positively with abdominal visceral adipose tissue area ( $r = 0.58$ ,  $P = 0.01$ ) and inversely with subcutaneous fat ( $r = -0.51$ ,  $P = 0.02$ ).

Statistical analysis did not link PI experience with increased lipolysis. But a multivariate analysis controlling for age, body mass index, and waist-to-hip ratio did identify two predictors of insulin resistance: use of d4T ( $P = 0.006$ ) and lipolysis rate ( $P = 0.02$ ). Grinspoon agreed with an attendee who observed that the correlation with d4T may reflect longer treatment duration rather than a specific drug effect. The main point, he stressed, is that increased lipolysis in men with visceral fat accumulation predicts insulin resistance. In other words, long-term fat buildup in people taking antiretrovirals, not just the immediate effect of protease inhibitors, favors insulin resistance.

Further work by Grinspoon’s group appeared to clinch the case for the role of lipolysis in insulin resistance [abstract 8]. This study involved seven insulin-resistant men averaging 3.6 years of PI experience. They had a mean waist-to-hip ratio of 0.99, and all had physical evidence of lipodystrophy. This time Grinspoon and coworkers ran frequent intravenous glucose tolerance tests after the study participants took either acipimox, a potent inhibitor of lipolysis, or placebo. Three to seven days later, they repeated the test after study participants got acipimox or placebo, depending on what they had received the first time. Investigators were blinded to the agent being used.

Compared with placebo, acipimox lowered free fatty acid levels by 40 percent (73 versus 122 mmol/L/270 min,  $P = 0.015$ ) and increased insulin sensitivity 84 percent. The free fatty acid area under the curve was inversely associated with insulin sensitivity ( $r = -0.75$ ,  $P = 0.05$ ). Grinspoon concluded that blocking lipolysis cuts free fatty acids and improves insulin sensitivity

in HIV-infected men with central adiposity. Simon Mallal and David Nolan's review of the workshop concurred that these findings support "a prominent role of adipose tissue in mediating whole-body insulin sensitivity in HAART-treated patients."<sup>1</sup> Grinspoon proposed that "long-term strategies to reduce free fatty acid concentrations may be useful in the treatment of the metabolic disturbances associated with HIV lipodystrophy."

The study included only men for a good reason: The lipolysis-blocking action of acipimox may be gender specific. So Grinspoon noted that his results may not apply to women. Indeed, the sharp-eyed reader will have noticed that all the human studies discussed so far involved only men. (Hruz's rats were guys too.) As Simon Mallal and colleagues observe in a recent review, the bulk of lipodystrophy studies presented to date involve mostly *white* men, so the results may not apply to others.<sup>4</sup>

Whereas Grinspoon's first study couldn't correlate PI experience with more lipolysis, a group from Washington University in St. Louis did link duration of both PIs and NRTIs to insulin resistance [abstract 6]. This study of 12 men with HIV infection, seven healthy young men ( $25 \pm 4$  years old), and nine healthy older men ( $69 \pm 5$  years old) also indicated that both hepatic and peripheral (fat and/or muscle) mechanisms contribute to insulin resistance in seropositive men with increasing trunk fat.

Intravenous glucose tolerance clearly reflected length of infection and treatment duration in the men with HIV infection. Kevin Yarasheski reported that four men with normal glucose tolerance had been infected for an average four years, whereas six men with impaired glucose tolerance and two with non-insulin-dependent diabetes mellitus both averaged 10 years of infection. Insulin sensitivity proved significantly lower in the men with impaired glucose tolerance or diabetes than in those with normal glucose tolerance or in the young or old healthy volunteers ( $P < 0.0007$ ). The study also showed an inverse correlation between insulin sensitivity and weeks of treatment with PIs or NRTIs ( $r^2 = 0.3$ ,  $P < 0.04$ ). In the men with impaired glucose tolerance or diabetes,  $\beta$ -cell sensitivity couldn't compensate for their insulin resistance. And all of the HIV-infected men had significantly lower hepatic insulin extraction rates than the healthy controls ( $P = 0.002$ ).

A case-control study of 18 men with lipodystrophy and 18 HIV-infected men

without the syndrome confirmed Yarasheski's finding of liver involvement in insulin resistance [abstract 5]. But this study did not find that treatment duration mattered in hepatic glucose production. Neither time taking NRTIs nor time taking PIs correlated with fasting hepatic glucose.

Steen Haugaard (Hvidovre University Hospital, Copenhagen) found increased fasting insulin in the men with lipodystrophy (84 versus 41 pM,  $P = 0.002$ ), but the two groups nearly mirrored each other in fasting hepatic glucose production (82 versus 80 mg of glucose/min/m<sup>2</sup>). Those findings "strongly suggested" to Haugaard and coworkers that the lipodystrophy group suffered from hepatic insulin resistance. But they also concluded that "peripheral insulin resistance is at least equally important in the defective insulin action" seen with lipodystrophy, because peripheral glucose disposal was significantly impeded in the lipodystrophy group (165 versus 238 mg of glucose/min/m<sup>2</sup>,  $P = 0.002$ ).

#### Insulin advice for clinicians? Not yet

So. What lessons can be fished from this wine-dark sea of data? As Kevin Yarasheski noted in one workshop roundtable, "We all agree that patients on PIs have insulin resistance, but we seem to differ on whether it's acute or chronic or where the glucose goes." Yet, taking the findings at face value, one might conclude that both acute and long-term mechanisms pull an oar in insulin resistance, though tracing glycemetic peregrinations through liver, muscle, and fat will require further Odyssean craft.

A more immediate question for clinicians is what insulin resistance means for a paunchy 45-year-old, and whether a little insulin resistance is as bad as a lot. As Steven Grinspoon observed after his report on lipolysis and insulin resistance, the protocol required severe insulin resistance for entry. Whether the results apply to people with "garden variety insulin resistance," he couldn't say. What clinical consequences insulin resistance may have in five or 10 years is even harder to figure.

In an interview with *IAPAC Monthly*, Grinspoon agreed that HIV clinicians may be missing insulin resistance in their patients, "because there's no one standardized test for insulin resistance, and some of the tests would require measurement of indices that clinicians aren't used to, such as insulin levels and performance of glucose tolerance tests." But he believes there's an

"increasing recognition" among HIV specialists and other physicians "that insulin resistance may contribute independently to cardiovascular risk."

At the same time, cohort studies indicate that hyperglycemia remains fairly infrequent among people taking antiretrovirals, and frank diabetes is rarer still. One five-year follow-up of 221 people before and after starting a PI found only 5 percent with new-onset hyperglycemia.<sup>5</sup> And only one third of that 5 percent came away with a diagnosis of diabetes mellitus.

A recent review of drug-induced hyperglycemia<sup>6</sup> proposes that:

- People beginning PI therapy should have a pretreatment fasting plasma glucose level and serum glucose readings every three or four months in the first year of therapy.
- People with a high risk of high glucose (see note 6) should have their glucose checked every six months for the duration of treatment.
- People whose plasma glucose stays in the normal range in the first year of treatment should have a yearly measure thereafter as long as antiretroviral therapy continues.

Grinspoon agreed that's a reasonable screening plan to make sure a person taking PIs doesn't end up with diabetes. But he stressed that just measuring glucose doesn't tell you about insulin resistance. At some point, he added, continuing research may show that it also pays to monitor for insulin resistance. But we're not there now.

The precise role of antiretrovirals in the long-term insulin resistance studied by Grinspoon, Yarasheski, and Haugaard also remains uncertain. The failure to link PIs with lipolysis in Grinspoon's study or with fasting hepatic glucose in Haugaard's certainly doesn't exculpate the drugs, because the studies are small. But PIs are not a *sine qua non* of fat accumulation in people taking antiretrovirals, as long-term follow-up of the Atlantic trial cohort showed.<sup>7</sup> So any conclusions about specific drug or class effects in the long-term scenario would be premature.



Most balletomanes know *agon* means contest or struggle because of Balanchine's

dance by that name. Curiously, though, the 12 dancers in this work don't do much struggling, preferring polite sarabandes, gaillards, and pas de deux. Balanchine even writes that the dance's title "was . . . the only Greek thing about the ballet."<sup>8</sup> But *agon* in all its ripeness informs medical jargon, with hushed talk of dying's agonal stage. And today pharmacologists best catch the contest in *agon* when referring to agonists that plow into receptors meant for others.

Some such agonists have earned close scrutiny as contestants in the struggle against lipodystrophy because they can ease insulin resistance. So all this insulin resistance research may make a difference for people with lipodystrophy by pointing the way to better therapy. If insulin resistance both starts soon and lasts long in people taking PIs, it may make sense to try other antiretrovirals first—in those predisposed to hyperglycemia, for example—or to refine treatments for metabolic disorders. In reviewing the Lipodystrophy Workshop at the 8th European Conference, Simon Mallal proposed that this new work on lipodystrophy's genesis could buttress "a shift away from growth hormone and anabolic steroid treatments" for this syndrome,<sup>1</sup> and a turn toward more precisely targeted insulin sensitizers—the glitazones and metformin.

Indeed, recombinant human growth hormone (rhGH) and anabolic steroids did not make a good showing at the Lipodystrophy Workshop. Kathleen Mulligan offered a close look at five people in a trial of rhGH given for six months at 3 mg daily [abstract 26]. She tracked significantly increased lipolysis and gluconeogenesis at months one and six, and a significant buildup of free fatty acid at month six. Although the lipid profile improved during rhGH therapy, 3 mg daily (half the dose used for AIDS wasting) spurred both hepatic and peripheral insulin resistance. One person suffered new-onset diabetes during the study.

Mulligan suggested doing a glucose tolerance test before trying rhGH and avoiding the drug as a fat accumulation remedy when the two-hour glucose measures 140 mg/dL or more. But in the roundtable after Mulligan's talk, session chair Ian Weller (Royal Free and University College Medical School, London) wondered whether rhGH should be used at all in people with lipodystrophy. Mulligan argued that, so far, rhGH is the only nonsurgical therapy that has consistently trimmed fat in people with

lipodystrophy, albeit in open-label studies. She noted that the best rhGH dose for lipodystrophy remains uncertain, and that the prudent will await results of ongoing placebo-controlled trials.

A nonrandomized observational study of 17 HIV-infected people taking testosterone cypionate and 23 who had never taken testosterone found significantly lower high-density lipoprotein (HDL or "good") cholesterol in the testosterone group ( $P < 0.05$ ) and significantly higher triglycerides, insulin, and C-peptide with testosterone ( $P < 0.05$ ) [abstract 62]. Peter Ford (Queens University, Kingston) reported that the groups didn't differ in age, smoking habits, weight, body mass index, waist-to-hip ratio, or diet. He concluded that the lipid and insulin changes in the testosterone group "can increase the risk of cardiovascular events."

The testosterone derivative oxymethalone, at 50 mg two or three times daily, did not change body fat in 60 people with HIV wasting or lipodystrophy, though it did improve body cell mass and lean body mass [abstract 70]. At the same time, Ulrich Hengge (University of Essen, Germany) recorded significant elevations in liver enzymes and glucose in 14 percent of those taking oxymethalone for 16 weeks.

### Glitazones: a paradox and a pair of studies

One pathway on which insulin drives formation of new adipocytes involves a fat cell factor called peroxisome proliferator-activated receptor  $\gamma$  or, for the memory challenged, PPAR- $\gamma$ . These little receptors with the big name play more than a bit part in manufacturing fat, explained Stephen O'Rahilly (University of Cambridge). Mice lacking the gene for PPAR- $\gamma$ , for example, just don't make fat.

PPAR- $\gamma$  gene knockouts may not be the best idea for humans, but PPAR- $\gamma$  agonists (activators) are already on pharmacy shelves in the guise of glitazones, more commonly known as insulin sensitizers. Why they help people with diabetes at first seems something of a paradox, O'Rahilly noted. Glitazones foster fat cell formation, and too much fat is a top cause of insulin resistance. Yet glitazones improve insulin sensitivity, perhaps because of what O'Rahilly calls "fat sculpting"—putting fat in safer places. Glitazones tend to trim unhealthy visceral fat and tack on subcutaneous fat. In theory, this dual action sounds ideal for many people with HIV lipodystrophy.

A problem with these drugs—potentially a big problem for lots of people with HIV infection—is liver toxicity. The best-studied agent in the class, troglitazone, got pulled from the market because of unhappy hepatic repercussions. But its successors, including rosiglitazone and pioglitazone, look safer. O'Rahilly claimed growing confidence in the clinical use of newer glitazones, even in people with liver abnormalities.

A theoretical framework for good glitazone activity in people with PI-induced insulin resistance came from a cell study by Jacqueline Capeau (Saint-Antoine Hospital, Paris) [abstract 24]. She found that half-maximal effective concentrations of indinavir, nelfinavir, and amprenavir stifled differentiation of 3T3-F442A adipocytes, with indinavir the worst offender, followed by nelfinavir, then amprenavir. Indinavir and, to a lesser extent, nelfinavir also prompted the death of fat cells that did form. But rosiglitazone reversed these inimical actions.

In six HIV-infected people with diabetes and lipodystrophy, troglitazone improved insulin sensitivity in four while adding subcutaneous fat and cutting visceral fat.<sup>9</sup> A larger study in seronegative people with congenital lipodystrophy showed similar benefits with troglitazone.<sup>10</sup> Now that troglitazone is history, how are the newer glitazones doing? The biggest study of rosiglitazone, with or without metformin in a placebo-controlled design (ACTG 5082), is still accruing participants. But pilot studies of rosiglitazone and pioglitazone debuted at the workshop. The good news is that both drugs looked safe in people with HIV lipodystrophy. The not-so-good news is that they didn't do much to improve metabolic markers or body shape over six months, but there may be a good explanation for that.

Alexandra Calmy (University Hospital, Geneva) gave pioglitazone to four women and five men with moderate to severe lipodystrophy [abstract 43]. Five were taking a PI when they started 30 mg of pioglitazone daily for three months; then they took 45 mg daily for another three months. At that point liver function tests showed no change from baseline. Nor were there substantial changes in weight (65.8 to 66.7 kg), waist-to-hip ratio (0.9 to 0.98), total cholesterol (6.4 to 6.3 mmol/L), or low-density lipoprotein (LDL or "bad") cholesterol (3.8 to 3.6 mmol/L). The average triglyceride reading dropped from 3.6 to

2.5 mmol/L, but that change lacked statistical significance. Four of the nine study participants thought their fat distribution improved, but self-reported fat improvements often prove unreliable. In this study DEXA scans disclosed no significant changes in total, arm, or leg fat mass.

Fehmida Visnegarwala (Baylor College of Medicine, Houston) unrolled a chart review of seven men and two women with physician-reported lipodystrophy who took rosiglitazone for a median of 24 weeks [abstract 124]. Five were taking a PI when they started the PPAR- $\gamma$  agonist at 4 mg daily; clinicians pushed that dose to 8 mg daily in five of the nine. No one stopped rosiglitazone because of liver toxicity.

Four people had improvements in facial fat wasting or thin arms and legs. But again those results are hard to assess, especially in a nonblinded study, because they were based on subjective evaluations by study participants and physicians, not on objective measures. Also, three of the four people who felt some fat improvement changed antiretrovirals; one dropped a PI and d4T, another dumped only a PI, and a third quit all antiretrovirals.

When Visnegarwala did look at the hard numbers, she found a reasonable, though not quite significant improvement in waist-to-hip ratio, from 1.02 to 0.95 ( $P = 0.08$ ). While total and HDL cholesterol changed little, triglycerides once more dropped substantially, but not significantly, from 818 to 370 mg/dL.

The biggest difference between these studies' results appears to be the change in waist-to-hip ratio. While it worsened in the pioglitazone study, it improved with rosiglitazone. This may not reflect a difference in activity of the two drugs, but a difference in study entry requirements. The people taking pioglitazone didn't have diabetes and had normal insulin sensitivity at baseline; those in the rosiglitazone study also had normal glucose levels, but they were all insulin resistant.

"These drugs modify insulin resistance, and that's what they're used for," Steven Grinspoon emphasized in a phone interview. "Secondarily they may affect body composition, but we can't bank on that yet." So while three months of troglitazone boosted subcutaneous fat and lowered visceral fat in four of six people with insulin resistance and diabetes,<sup>9</sup> pioglitazone had little measurable effect after six months in people without insulin resistance. Six months of

rosiglitazone seemed to do better in trimming waist fat of people with insulin resistance, but still without hyperglycemia. Insulin resistance didn't improve much in that study. But it's inappropriate to draw any conclusions from small open-label studies, one of them a chart review.

### **Metformin: no panacea, but potent in the right population?**

Two studies looked at metformin in people with lipodystrophy, with different results. But again study entry criteria may explain some of the difference. Steven Grinspoon's group offered an update of their randomized, double-blind, placebo-controlled study of metformin.<sup>11</sup> Everyone in the metformin group and most in the placebo group were taking a PI. In the three-month blinded phase of the trial, the 14 people receiving metformin (500 mg twice daily) had a significant drop in insulin two hours after an oral glucose tolerance test ( $P = 0.01$ ), and significantly reduced weight ( $P = 0.005$ ) and diastolic blood pressure ( $P = 0.009$ ), compared with 12 people taking placebo. Visceral abdominal fat also fell in the metformin group, though not significantly ( $P = 0.08$ ), while waist circumference did shrink significantly with metformin (mean -1.1 cm,  $P = 0.02$ ). Further study of these individuals showed that metformin improved markers of fibrinolysis and cardiovascular risk.<sup>12</sup>

At the Lipodystrophy Workshop, Grinspoon reported results in 11 people from the metformin group who took the drug in an open-label six-month extension and nine in the placebo arm who started metformin after month three [abstract 69]. People originally randomized to metformin were eligible to continue treatment only if they had at least a 15 percent improvement in glucose tolerance or fasting hyperinsulinemia at three months. Three of them upped their dose to 850 mg twice daily.

Everyone in the original metformin group maintained a significant drop in insulin area under the curve through nine months (-3066  $\mu\text{U}/\text{mL}/120$  min,  $P < 0.04$ ). The eight placebo-group participants who took metformin for six months enjoyed a similarly significant slump in insulin (-3404  $\mu\text{U}/\text{mL}/120$  min). Both groups also had significant drops in glucose area under the curve after nine months (-1231 mg/dL/120 min in the original metformin group and -1506 mg/dL/120 min in the original placebo group,  $P < 0.05$ ). But

people who took metformin for nine months outpaced those who took it for six months in improved waist-to-hip ratio, waist circumference, and percent trunk fat.

Three quarters of study participants suffered from diarrhea, which resolved in three to six months. High lactates are a worrisome side effect of metformin, but lactate levels stayed flat in all study participants, and no one quit because of toxicity. Another concern with metformin is its tendency to trim subcutaneous fat, as it did in the three-month blinded phase of this study, so it may worsen lipodystrophy in people already suffering from that aspect of lipodystrophy.

A one-year, double-blind, placebo-controlled trial of metformin or gemfibrozil in people with PI-associated lipodystrophy found no anatomical benefit for either drug and no significant improvement in metabolic markers [abstract 29]. Esteban Martínez (Hospital Clinic, Barcelona) randomized people with abdominal fat buildup and triglycerides above 200 mg/dL to take 850 mg of metformin twice daily, 600 mg of gemfibrozil twice daily, or a twice-daily placebo. Average waist-to-hip ratios were high and consistent from group to group, ranging from 0.93 to 0.95.

After 12 months on their assigned regimen, few of the 46 people who completed the study met the primary endpoint—a waist-to-hip ratio of 0.8 or less for women or 0.9 or less for men. Martínez reported that 14 percent taking metformin, 17 percent taking gemfibrozil, and 15 percent taking placebo reached that goal. Between-group differences were not statistically significant. Body mass index did not change significantly in any of the groups; neither did triglycerides, total cholesterol, LDL, or HDL. Insulin area under the curve did improve more with metformin than with gemfibrozil or placebo, but not significantly so.

Number-savvy Andrew Hill (Roche) suggested that the study may have been too small to detect statistically significant differences between groups, and Martínez conceded that possibility. Yet the study was no smaller than Grinspoon's placebo-controlled metformin study,<sup>11</sup> which did find a significant three-month drop in insulin with metformin. The critical difference may be that insulin resistance was an entry requirement in the Grinspoon trial but not in the Martínez study. As pointed out by Stefan Mauss (Clinic for HIV, Düsseldorf), Martínez's exclusion of people with

impaired glucose tolerance barred the very patients who have responded best to metformin in the literature.

In the interview with *IAPAC Monthly*, Grinspoon stressed that insulin sensitizers like metformin and glitazones should be judged primarily for their effect on insulin, not for their ability to change body shape. Although waist circumference improved with metformin during the blinded and open-label parts of his study, he doesn't see body shape changes as a primary goal of therapy. In his study "visceral fat went down," Grinspoon said, "but this was not the primary endpoint."

"Patients may not like the idea of taking a drug to modify things they can't feel or see," Grinspoon added, and that could be a problem if further study shows insulin sensitizers don't have a big impact on body shape. Because people don't feel insulin resistance any more than they feel high blood pressure, he explained, adherence to metformin or glitazones may be as chancy as adherence to antihypertensives.

Still, Grinspoon said, "I remain quite hopeful for these drugs" in HIV-infected people with insulin resistance. "But I think these preliminary studies are telling us that we can't just apply them indiscriminately to the entire population."

Simon Mallal was less sanguine about metformin's prospects for people with HIV lipodystrophy. "I don't think it's the panacea we've been waiting for," he told attendees of the 8th European Conference. In his printed review of the Lipodystrophy Workshop, he also noted that fibrates like gemfibrozil "would be predicted to have limited efficacy" for lipodystrophy if faster fat oxidation turns out to be a major component of this syndrome.<sup>1</sup> The problem is that fibrates act primarily by increasing fat oxidation, Mallal wrote, so they won't do much if fat oxidation is already in overdrive.

### **Fibrates and statins: clinical role still murky**

Though gemfibrozil disappointed as a lipid-lowerer in the Martínez study (see preceding section), a retrospective review of 103 people taking fibrates (mostly gemfibrozil) or statins for PI-linked hyperlipidemia concluded that fibrates may be "an attractive first choice for management of HIV dyslipidemia" [abstract 30]. But statins were less impressive in this analysis. And because few people met standard cholesterol or triglyceride tar-

gets, Fehmida Visnegarwala (Baylor College of Medicine, Houston) concluded that it is "unclear whether [HIV-related] dyslipidemia can or should be managed by using National Cholesterol Education Program<sup>13</sup> guidelines."

The study included just over 100 consecutive patients with antiretroviral-linked dyslipidemia who took one or more lipid-lowering agents for a median 44 weeks. Most of the regimens, 90 percent, included gemfibrozil, while 49 percent included atorvastatin, 20 percent pravastatin, 19 percent simvastatin, 12 percent lovastatin, and 10 percent fenofibrate.

Among 77 people who took only a fibrate (gemfibrozil or fenofibrate), the median triglyceride level fell 40 percent and the median total cholesterol dropped 7 percent ( $P < 0.001$  for both). HDL cholesterol did not change significantly. In the 20 people who took both fibrates and statins, median triglyceride and cholesterol drops measured 42 percent ( $P = 0.04$ ) and 14 percent ( $P = 0.002$ ). Among 38 people who took only statins, only triglycerides fell significantly, by 14 percent ( $P = 0.02$ ).

Looking at the results another way suggested a less robust response regardless of the antilipid agents used. Only 13 of 66 who started with a total cholesterol above 240 mg/dL reached a target of less than 200 mg/dL, and five of the 13 had stopped their PI. Only 12 of 64 who started with triglycerides above 400 mg/dL ended up under 200 mg/dL, and six of the 12 had stopped their PI.

In a multivariate analysis involving 33 people with a good cholesterol response, only stopping a protease inhibitor predicted such a response (odds ratio 10.7,  $P = 0.004$ ). Nonpredictive variables were treatment with fibrates or statins, baseline cholesterol below 300 mg/dL, baseline triglycerides below 400 mg/dL, adherence to antilipid therapy, age, gender, race, current diabetes mellitus, and number of cardiovascular risk factors.

Like all retrospective studies, this one suffers from its inability to control certain variables. Visnegarwala pointed out two such soft spots: She could define nonadherence only as missing one or more refills at the pharmacy. And she couldn't account at all for possible lifestyle changes. Carl Grunfeld (University of California, San Francisco) picked up on the latter shortcoming, noting that lipid-lowerers do little without dietary control in people with

baseline lipids as high as those in this group (means of 281 mg/dL for cholesterol and 836 mg/dL for triglycerides). Visnegarwala agreed, but she added cogently that the Baylor lipid clinic has a full-time dietician, so the level of care these people received probably equals or exceeds that in most HIV clinics. If that assessment is correct, controlling high lipids in people taking PIs figures to be tougher than controlling high viral loads.

A 16-person, randomized, placebo-controlled trial of fluvastatin (40 mg daily) in PI-treated people with hyperlipidemia found a significant drop in total cholesterol (from 8.0 to 6.6 mmol/L,  $P < 0.001$ ) after 28 days of treatment, but not in triglycerides. Vincent Mooser (Lausanne University Hospital) divulged these data as part of a plenary talk on PIs and cardiovascular risk, adding that fluvastatin had no substantial interactions with the PIs being used.

Graeme Moyle (Chelsea and Westminster Hospital, London) saw similar results in his published 24-week trial of pravastatin plus dietary advice versus dietary advice alone.<sup>14</sup> But he wondered whether these drops in cholesterol, though significant, translate into a meaningful clinical benefit. Moyle noted that researchers who ran a pravastatin prevention trial in people with endogenous hyperlipidemia figured that thousands of people would have to take this drug for five years before a clinical benefit could be measured.<sup>15</sup> At this point in statin research, he asked, are we treating our patients or are we treating their blood levels?



**CATACLYSM  
(WHICH REGIMENS  
RAISE HEART RISKS?)**

The answer to Graeme Moyle's question about antilipid therapy for people on PIs (see preceding paragraph) may lie in continuing studies of heart disease risk with HAART. And studies of that ilk at the Athens meetings didn't draw a consistent picture. Even if one assumes the worst-case scenario—that protease inhibitors dangerously inflate the background risk of heart disease—deciding how to counter that threat isn't easy. In an interview with *IAPAC Monthly*, Steven Grinspoon posed the dilemma this way:

"Do you add on a new medicine to treat

insulin resistance,” or high cholesterol or triglycerides, he might have added, “or do you try to change the antiviral regimen to ameliorate it that way?”

Some leading clinical researchers, like William Powderly at Washington University in St. Louis, now lean toward stopping the PI in favor of an NNRTI or abacavir, or at least staying away from first-line PIs, when someone with HIV infection already has a few coronary risk factors. “It seems increasingly apparent that the choice of antiretroviral therapy must be, in part, influenced by factors other than HIV,” Powderly wrote in a recent review.<sup>16</sup> “In particular, cardiovascular risk factors such as family history, smoking, hypertension, diabetes mellitus, and preexisting hyperlipidemia should influence choice of treatment.”

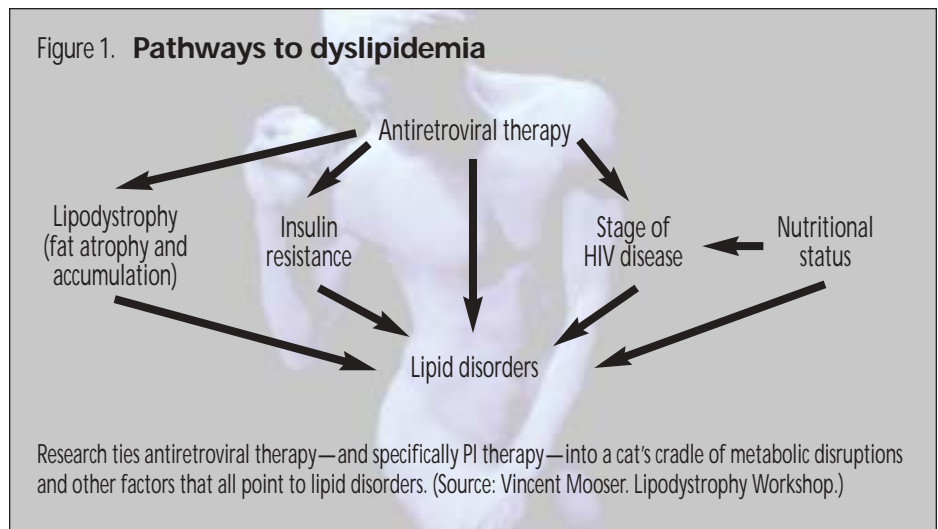
But research unveiled in Athens did not invariably support this tack. Though one might cite the growing mound of cohort and open-label data showing better first-line responses to efavirenz than to PIs<sup>17-19</sup> and ask, Why not just start with this once-daily nonnucleoside, avoid the PI toxicity, and get a better antiviral punch too? The answer, pasted together from Athens posters, may be, because heart risks aren’t lower in some NNRTI cohorts, and because efavirenz takers have cholesterol problems of their own.

But this highly post-Socratic dialogue hardly begins to probe the complex questions raised in the free-wheeling agora of PI-versus-non-PI polemics.

### “Some reasons to be worried”

“Will the beneficial effects of [PI-based] HAART be offset by a cardiovascular disease epidemic?” asked Vincent Mooser at the Lipodystrophy Workshop. Assigned to answer that question by workshop organizers, Mooser allowed that “there are some reasons here to be worried.”

Mooser proposed that antiretroviral therapy, and PI treatment in particular, stands atop a cascade of disorders and cofactors that ultimately spills into a pool of dysregulated lipids (Figure 1). And he placed those roiling lipids near the origin of an atherogenic flow chart that ended with the words fatty streak, plaque, rupture, thrombosis, and cardiovascular events. Although prospective studies aiming to pin down PIs’ role in these “events” are under way, the current lack of prospective data made Mooser caution that “I’m walking on soft ground” in rating the PI risk. “So



don’t get mad at me if this doesn’t happen in the next few years.”

To be sure, Mooser’s roadmap to cardiovascular cataclysm included many a way station that has nothing to do with antiretrovirals (such as aging, smoking, and chronic infection and inflammation) as well as some signposts that may or may not involve HIV meds (like hypertension and diabetes). And when Mooser did a case-control study of Swiss people with or without HIV infection, the independent predictors of plaque formation were age, cholesterol, cigarette smoking, and gender—but not PI therapy.

This study compared 168 HIV-infected individuals with 68 seronegative controls who came to an anonymous HIV testing clinic but tested negative. The HIV group was slightly but significantly older than the controls (39 versus 37 years,  $P = 0.04$ ), and more people with HIV smoked (61 versus 46 percent,  $P = 0.03$ ) and had high lipids (56 versus 24 percent,  $P < 0.01$ ).

Mooser used ultrasound to see who had arterial plaques and who didn’t. A multivariate analysis for plaque risk set odds ratios of 11.4 for age (oldest quartile versus youngest quartile,  $P < 0.001$ ), 4.4 for cholesterol above 8 mmol/L ( $P = 0.03$ ), 3.1 for cigarette smoking ( $P = 0.001$ ), and 2.4 for male gender ( $P = 0.02$ ). HIV infection and PI therapy did not independently raise the risk of plaques. The analysis underlines the difficulty of plucking PIs from a list of risk factors—then either implicating or exonerating them—since they may well have contributed to the doubled rate of hyperlipidemia in the HIV-infected group.

A French comparison of HIV-infected men taking PIs and an age- and weight-matched cohort of seronegative men also

accented the mélange of risk factors that challenges simple analysis in any population [abstract 112]. Even though the 223 men taking mostly single-PI therapies had significantly lower blood pressure ( $P = 0.003$ ) and fasting blood glucose ( $P < 0.0001$ ) than the control group, they had a higher five-year risk of coronary heart disease (CHD), with risk ratios of 1.2 and 1.39, depending on the variables in the model ( $P < 0.000001$  for both models). The problems for the PI group, reported Marianne Savès, were higher waist-to-hip ratios, higher cholesterol, lower HDL, and more smoking than in the control group ( $P < 0.0001$  for all comparisons).

This analysis and Mooser’s Swiss case-control comparison are not the first studies to pinpoint smoking as a frequent risk factor in Europeans with HIV infection. While the Swiss study did not tie PIs directly to plaque formation, the French comparison does imply a bond between PIs and higher coronary risk because of the wider waists and higher lipids in the PI group (34 percent were taking nelfinavir, 32 percent indinavir, and 14 percent ritonavir). Yet the lower blood pressure and glucose in the PI-treated men show that risk trends don’t run in the same direction in every HIV cohort.

A single-center chart review, at Ramón y Cajal Hospital in Madrid, drew an interesting distinction between HIV-infected people who suffered ischemic heart disease or central nervous system vascular disease before and during the HAART era [abstract 52]. Antonio Antela cataloged nine cases from 1994 to 1997 and 14 from 1998 to 2000. (Unfortunately he didn’t compare the prevalence of cardiovascular disease in the two groups.) Only three of nine people in the 1994-1997 cohort had taken

antiretrovirals, dual NRTIs in all cases. Nine of the 14 people in the later group had taken an antiretroviral regimen (for a median 29 months), eight of them including a protease inhibitor. Everyone in the earlier group died, eight from AIDS. The only person in the later group who died was a 74-year-old man who had a stroke.

Both groups had high rates of classic cardiovascular risk factors, including heavy smoking by all nine in the pre-HAART group and by 11 of 14 in the HAART group. But the PIs may have added to the risk in the later group, which included five people with dyslipidemia and one overweight person. Still, Antela and colleagues stressed that “the administration of HAART confers longer survival after the development of a cardiovascular complication.” At least within the time frame of this chart review, HAART kept people from dying rather than hastening their death through side effects, while everyone in the pre-HAART group died, almost always from AIDS and never from vascular disease.

Another Spanish study, from Barcelona’s Santa Creu i Sant Pau Hospital, found no difference in 10-year CHD risk between 159 people taking a PI regimen and 253 taking an NNRTI or triple nucleosides, even though the PI group had significantly more smokers than the non-PI group (64.6 versus 52 percent,  $P = 0.02$ ) [abstract 51]. The analysis is limited though, because Pere Domingo and coworkers didn’t report how many people in the PI-sparing groups had switched from PI therapy.

Using the Framingham formula to calculate CHD risk, these investigators did find a higher 10-year risk in people with lipodystrophy (7.7 percent) than in those without it (6.4 percent), a nearly significant difference ( $P = 0.07$ ). Contrary to expectations, lipodystrophy rather than lipohypertrophy drove this difference. The 10-year CHD risk was 6.9 percent among people with fat hypertrophy and 6.9 among those without it. But the risk for people with lipodystrophy came to 7.9 percent, compared with 6.3 percent for people without atrophy ( $P = 0.02$ ).

A huge cohort study involving 17,852 people with HIV infection failed to distinguish between PI and NNRTI regimens when using total cholesterol as the yardstick [abstract O18]. As in Domingo’s report, the D:A:D study did not look at people treated *only* with a PI regimen or *only* with an NNRTI combination. Nearly

three quarters of enrollees from nine distinct cohorts did in fact have PI experience (for a median 2.8 years), whereas 40 percent had taken an NNRTI (for a median 1.3 years).

In the group now taking a nonnucleoside, 22 percent had a total cholesterol above 6.2 mmol/L, as did 25 percent taking a PI. Nina Friis-Møller reported that 45 percent taking an NNRTI with a PI—presumably those with more advanced disease and more treatment experience—had a cholesterol reading above 6.2 mmol/L. Indeed, a multivariate analysis correlated duration of PI and NRTI therapy, older age, and lipodystrophy with high cholesterol. Friis-Møller promised that the D:A:D team would present more refined analyses as the research continues.

At the Lipodystrophy Workshop, Dusseldorf clinician Stefan Mauss showed just how complicated it can be to predict risk from total cholesterol numbers [abstract 86]. He found that 48 percent of 172 consecutive patients had a total cholesterol above 200 mg/dL (5.17 mmol/L). But two thirds of this 48 percent had high very low-density lipoprotein (VLDL) cholesterol and normal LDL. Because “VLDL contains about 20 percent cholesterol in addition to triglycerides,” Mauss explained, “the increased concentration of VLDL leads to an elevated total cholesterol.” The relatively low rate of high LDL in this group, he argued, could mean “the cardiovascular risk in the majority of HIV-positive patients with hypercholesterolemia may be lower than expected from total cholesterol.”

But wait. There’s yet another way to parse this lipid profile, suggested Simon Mallal in his review of the workshop.<sup>1</sup> Mauss’s results, Mallal proposed, “may also be interpreted as confirming a high prevalence of insulin resistance in this population, and [as a result] the development of an atherogenic metabolic profile that is not predicted by LDL cholesterol.”

A multicenter German study presented by Armin Goetzenich (DAGNÄ, Aachen) underlined the need for more detailed analysis to estimate toxicities of individual drugs [abstract P109]. This cross-sectional study involved 39 people who took nevirapine at any point since 1996 (median duration 9.7 months) and 38 who took efavirenz at any time (median duration 5.8 months). Comparing these individuals with 221 people who never took a nonnucleoside, Goetzenich and colleagues linked NNRTI

treatment for more than 12 months with an 80 percent lower risk of lipodystrophy. In the same analysis d4T raised the risk of lipodystrophy 2.52 times and a CD4 nadir below 200 cells/mm<sup>3</sup> raised the risk 2.21 times.

Looking only at people who had taken nevirapine or efavirenz, the German clinicians found a significant correlation between efavirenz and high cholesterol (relative risk 2.346,  $P = 0.007$ ). Nevirapine didn’t boost the risk of hypercholesterolemia and tended to lower the risk of high triglycerides (relative risk 0.551,  $P = 0.062$ ).

### Cardio events and carotid concerns

Several studies presented in Athens, and one reviewed at a US meeting, saw worrisome cardiovascular consequences of HIV infection in general, PI therapy in particular, and lipodystrophy in women.

A study using California Medicaid claims for HIV infection, antiretroviral therapy for more than 30 days, and a diagnosis of myocardial infarction, ischemic heart disease, angina, or coronary atherosclerosis found evidence of accelerated atherosclerosis in younger but not older HIV-infected men compared with seronegative men [abstract 49]. Judith Currier (University of California, Los Angeles) and coworkers winnowed through claims of 23,672 men with HIV and more than a million HIV-negative men filed between July 1994 and June 2000.

For the HIV group between 18 and 24 years old, the relative risk of CHD was three times higher than in their seronegative age-group counterparts. HIV-infected men aged 25 to 34 years had a two times higher risk than their age-matched non-HIV controls. And 35- to 44-year-olds with HIV infection had a 15 percent higher risk than seronegative men of their age. Older men with HIV actually had lower CHD risks than uninfected men, perhaps because more had died of AIDS, especially from 1994 to 1996, before heart disease could arise.

Currier pointed out that this kind of analysis can’t distinguish between the possible roles of chronic HIV infection, its treatment, or other factors in contributing to CHD. Data on smoking or family history, for example, could not be culled from Medicaid claims. And since Medicaid covers low-income people, CHD rates could be different in wealthier people with better health care, regardless of HIV

serostatus. It's also important to note that CHD rates per 100 person-years were not astronomical even in the high-risk younger HIV groups: 0.3 for 18- to 24-year-olds, 1.31 for 25- to 34-year-olds, and 1.51 for 35- to 44-year-olds. Respective rates for those three seronegative age groups were 0.1, 0.64, and 1.32.

Two studies did find links between PI treatment and myocardial infarction or other acute cardiovascular episodes. Comparing 3,013 people taking PIs with 2,665 not taking PIs in the ongoing HIV Outpatient Study (HOPS), US researchers figured an incidence of 1.2 per 1,000 person-years for infarction, angina, or stroke in the PI group. The incidence measured 0.5 per 1,000 person-years in the non-PI group.<sup>20</sup> A higher risk in the PI group held true even after statisticians accounted for other cardiovascular risk factors, though most of these episodes involved people with other heart disease risks.

At Milan's Sacco Hospital, Paola Meraviglia counted 14 acute cardiovascular episodes among 600 HIV-infected people monitored since 1997 [abstract 90]. All were taking a PI at the time, including nine on indinavir and two on a ritonavir-boosted regimen. Only three of these 14 people smoked, and one other person had a non-PI risk factor, an intravascular catheter. Four people had PI-related lipid elevations. These 12 men and two women averaged only 272 days of PI experience, but that experience ranged from 24 to 1,440 days.

At the Clinic of Infectious Diseases in Bari, Paolo Maggi and colleagues found a higher rate of new carotid lesions in 75 people taking a PI (57 percent) than in 25 PI-naïve people taking a nonnucleoside (16 percent) or 50 PI-naïve people taking a double NRTI regimen (14 percent) [abstract P125]. Everyone had taken their current regimen for at least 12 months, but the PI group had at least two baseline disadvantages: Their median age was 37 years (versus 35 for the NNRTI group and 34.5 for the NRTI group), and they had been infected with HIV longer (seven years versus four for the NNRTI group and 5.5 for the NRTI group). Maggi didn't report whether these differences were statistically significant. He correlated PI use, cigarette smoking, hypertriglyceridemia, and CDC disease stage with a higher risk of carotid lesions, but he didn't present details of that analysis.

Stephanie Wilkie in Steven Grinspoon's

Massachusetts General group found higher carotid intima media thickness in 22 women with HIV lipodystrophy than in age- and race-matched women in the general population [abstract 125]. This study found no link between thicker carotid walls and smoking or treatment with PIs or other antiretrovirals. But it correlated intima media thickness with age, diastolic blood pressure, body mass index, and fasting insulin.

For 10 Caucasian women in the lipodystrophy group, carotid intima media thickness averaged 0.62 mm, significantly greater than in Caucasian women of the same age (45 years) in the Framingham cohort ( $P = 0.01$ ). Eight African-American women in the lipodystrophy group also had significantly thicker carotid linings than age-matched African-American women in the Framingham cohort ( $P = 0.04$ ). In fact, intima media thickness in the women with lipodystrophy approached values for Framingham cohort women who were 10 years older.

"In this population," Grinspoon said at the workshop, "increased intima media thickness suggests an increased risk of cardiovascular disease."



## EPHEMERA (EPHEMERAL SYMPTOMS, EPHEMERAL RESULTS?)

While delicate cell probes and king-size cohort analyses try to tweeze out which drugs may spur which toxicities, antiretroviral start and switch studies plow ahead in attempts to prove some metabolic advantage. At least a score of such studies presented at or around the time of the Athens meetings weighed competing combinations for their effects on lipids, body fat, bones, lactates, and mitochondrial DNA. None of these studies answered—and few addressed—the most critical question about regimens that sidestep this or that complication for, perhaps, 48 weeks: Are observed differences in lipids, lactates, or bones clinically meaningful, or merely numeric?

The gods' emissaries blithely dismissed humans as ephemerals, which entomologists and fishermen know today as the short-lived mayfly. But, fresh from the hatch, the mayfly must sense nothing but long, luxurious life ahead, as it idles time away at the river's margin, finding mates, and mating—just as we do in our youth—and

even middle age. The standard of reference may be minutes for mayflies and years for humans, but we both commit this temporocentric fallacy. And clinical researchers do so all the time, not in laxity, but because the times demand fast answers. So 48 weeks look like a lifetime. Yet it took two steady years of PI use to uncover lipodystrophy, and a decade's worth of NRTIs to chronicle lipoatrophy. Thus the trick becomes reading the 48-week script in context, before the infinite black night in the trout's belly.

## Can abacavir avert or reverse lipodystrophy?

Preliminary results of a planned 96-week trial showed improved or barely changed lipids with abacavir plus Combivir (AZT/3TC), while Combivir/nelfinavir (1250 mg twice daily) and d4T/3TC/nelfinavir did push some lipid numbers in the wrong direction [abstract 27]. Study organizers deserve credit for recruiting as many treatment-naïve women as men for this open-label, randomized trial. But Lipodystrophy Workshop attendees criticized release of the 24-week data, fearing it could sway therapeutic decisions by participating clinicians and patients. Perhaps the investigators sought to dodge this problem by avoiding statistical comparisons of the 24-week results. But that only clouded the data's interpretation.

Princy Kumar (Georgetown University, Washington, DC) reported that the 86 people randomized to Combivir/abacavir, the 89 randomized to Combivir/nelfinavir, and the 83 randomized to d4T/3TC/nelfinavir started treatment with similar CD4 counts (medians in the 300s), similar viral loads (medians about 4.5 logs), and similar total cholesterol, LDL cholesterol, and triglycerides. All the median starting lipid levels were in the normal range (Table 1).

After 24 weeks, fasting LDL (the 96-week primary endpoint) fell an average 1.58 mg/dL in the Combivir/abacavir group while rising 14 mg/dL with Combivir/nelfinavir and 21.6 mg/dL with d4T/3TC/nelfinavir. Average LDL changes were similar for women and men. Total cholesterol gains for the three groups at 24 weeks measured 5.8, 21.6, and 29.3 mg/dL respectively, while triglycerides rose 7.7, 7.5, and 24.2 mg/dL. Kumar said the investigators couldn't explain why lipid changes were consistently worst in the d4T/3TC/nelfinavir arm. Still, median 24-

Table 1. **Mean lipid changes after 24 weeks of Combivir/abacavir and other regimens**

		Total cholesterol (mg/dL)	LDL cholesterol (mg/dL)	Triglycerides (mg/dL)
Normal or reference range		<200	60 – 130	10 – 190
Combivir/abacavir	Baseline	160.3	99.3	121.7
	24 weeks	166.1	97.7	129.4
Combivir/nelfinavir	Baseline	169.2	101.1	141.1
	24 weeks	190.8	115.1	148.6
d4T/3TC/nelfinavir	Baseline	166.1	100.5	137.3
	24 weeks	198.4	122.1	161.5

Source: Princy Kumar, abstract 27.

week levels of total cholesterol, LDL cholesterol, and triglycerides remained in the normal range in all three study arms.

In a 24-week missing-data-equal-failure analysis, similar proportions in the three arms had viral loads below 50 copies/mL, though Combivir/abacavir seemed to be doing *better* than the other regimens in people who began treatment with a viral load above 100,000 copies/mL (67, 58, and 43 percent below 50 copies/mL for the three arms). On the other hand, the median CD4<sup>+</sup> gain at week 24 was lowest with Combivir/abacavir, 90.5 cells/mm<sup>3</sup>, versus 132.5 cells/mm<sup>3</sup> for Combivir/nelfinavir and 137.5 cells/mm<sup>3</sup> for d4T/3TC/nelfinavir.

Another study of abacavir, AZT, and 3TC—this time as the three-in-one pill Trizivir in people switching from a first-line PI—found improved lipodystrophy symptoms and lowered lipids compared with continued PI treatment [abstract 28]. Again, though, a devil’s advocate might question the clinical import of these changes in a 48-week open-label study.

Alain Lefeuvre (Chalucet Hospital, Toulon) and coworkers randomized 103 people to continue their PI and 106 to switch to Trizivir. Both groups had taken antiretrovirals for about two years, and no one in either arm ever suffered a virologic failure. Everyone had a viral load below 400 copies/mL for at least six months and below 50 copies/mL at screening. After 48 weeks an intent-to-treat analysis figured that 75 percent in the Trizivir arm and 69 percent in the continued-PI group still had a sub-50 viral load.

At baseline 50 percent in the PI group and 40 percent assigned to Trizivir had one or more commonly recognized lipodystrophy symptoms, a nonsignificant difference. But 48 weeks later, significantly more in the continued-PI group (42 percent) than

in the Trizivir (28 percent) had at least one symptom ( $P = 0.03$ ). The difference could be explained by trends toward fewer new symptoms in the Trizivir arm (13 percent versus 23 percent for the PI arm,  $P = 0.078$ ) and more symptom resolution with Trizivir than with a continued PI (67 percent versus 42 percent,  $P = 0.059$ ). Fifteen people randomized to Trizivir (63 percent) and 13 randomized to stick with their PI (34 percent) saw at least one symptom resolve and added no new symptoms ( $P = 0.029$ ).

Some battle-weary clinicians may arch a brow at the high 48-week rate of symptom resolution in *either* arm of this study. In the steady-PI arm, 10 (26 percent) enjoyed resolution of at least one fat buildup symptom, and 12 (32 percent) bid adieu to at least one atrophic symptom. Respective numbers in the Trizivir group were nine (38 percent) and 10 (42 percent). Why even the continued-PI group had so much improvement remains unclear. One possibility must be considered: body fat changes were rated by study physicians, not by DEXA or CT or waist-to-hip ratio, and this was an open-label study.

Lefeuvre and colleagues also tracked total cholesterol and triglycerides throughout the study. At randomization median cholesterol was borderline high in both groups, 5.9 mmol/L for the Trizivir group and 5.6 mmol/L for the PI arm. At the 48-week mark, median cholesterol had dropped significantly more in the Trizivir group (by 0.8 mmol/L versus 0.44 mmol/L for the PI arm,  $P < 0.001$ ). It is interesting, though, that the medians for both groups ended up in the “desirable” range (Table 2), at 5.1 mmol/L for Trizivir and 5.16 mmol/L for continued PIs. Triglycerides dropped with Trizivir (by 0.17 mmol/L) and edged up with a continued PI (by 0.1 mmol/L), a significant difference ( $P < 0.001$ ). But in

both groups median triglycerides started and ended in the normal range (1.43 mmol/L for Trizivir and 1.7 mmol/L for the PI arm).

The better cholesterol levels in both groups and the clinically innocuous triglyceride difference suggest that study participants may have benefited as much from the greater care afforded in a clinical trial as from their assigned treatment. Yet if people in this study agreed with their clinicians about body shape improvements, then those switching to Trizivir gained at least a psychological edge over their PI-taking counterparts.

A nonrandomized study of PI-treated people who stayed with their protease drug, switched to abacavir or efavirenz, or quit antiretrovirals altogether confirmed the good lipid shifts with abacavir in Lefeuvre’s Trizivir study [abstract 75]. But glucose continued to rise after the abacavir switch, and people opting for efavirenz enjoyed no lipid or glucose benefit. Kristina Koppel (Söder Hospital, Stockholm) reported that insulin levels stayed put in the 122 people who continued a PI for two years, in 37 who switched to efavirenz for a median 10 months, and in 32 who switched to abacavir for a median nine months.

This prospective follow-up affords some insight into how much these values change in people continuing a PI regimen. Triglycerides rose significantly over two years of PI treatment but remained in the normal range (from 1.9 to 2.1 mmol/L,  $P = 0.005$ ) (Table 2), while total cholesterol inched upward through the “borderline high” bracket (from 5.7 to 5.9 mmol/L,  $P = 0.07$ ). Neither HDL nor LDL cholesterol changed significantly in these 122 people. Glucose climbed significantly, from 5.2 to 5.4 mmol/L ( $P < 0.001$ ) but stayed within the normal range. So, on a population level in a fair-sized HIV clinic, lipids and glucose rose significantly during two years of PI therapy, but those statistically significant changes could be called clinically modest.

Among the 32 people who switched from a PI to abacavir for a median nine months, total cholesterol for the group fell significantly from 5.7 to 5.2 mmol/L ( $P < 0.001$ ), a change that brought cholesterol close to the “desirable” level of 5.17 mmol/L (Table 2). An LDL plunge from 4.1 to 3.1 mmol/L ( $P = 0.002$ ) drove the total cholesterol drop and did bring the group’s LDL into the normal range. Glucose continued to climb, from 5.2 to

**Table 2. Normal and high lipid and glucose levels**

	Conventional units	SI units
Total cholesterol		
Desirable	< 200 mg/dL	< 5.17 mmol/L
Borderline high	200 – 239	5.17 – 6.20
High	≥ 240	≥ 6.21
LDL reference range	60 – 130 mg/dL	1.55 – 3.37 mmol/L
HDL reference range		
Male	35 – 65 mg/dL	0.91 – 1.68 mmol/L
Female	35 – 80 mg/dL	0.91 – 2.07 mmol/L
Triglyceride reference range	10 – 190 mg/dL	0.11 – 2.15 mmol/L
Glucose reference range (serum or plasma)	70 – 110 mg/dL	3.9 – 6.1 mmol/L
Insulin reference range (plasma)	11 – 240 µU/mL	79 – 1722 pmol/L

Source: Lantz JC et al. *American Medical Association Manual of Style*. 9th edition. Baltimore: Williams & Wilkins. 1998:486-503.

5.6 mmol/L ( $P < 0.001$ ), remaining in the normal range.

In the group of 37 who switched to efavirenz, the only lipid value that changed significantly during a median 10 months on the NNRTI was salubrious HDL cholesterol (from 1.2 to 1.3 mmol/L,  $P = 0.001$ ). Glucose also rose significantly (from 5.5 to 5.6 mmol/L,  $P = 0.002$ ) but stayed within the normal range.

Finally, Koppel tracked these measures in 31 people who stopped taking antiretrovirals for a median nine months. Average total cholesterol fell from the borderline high bracket (5.7 mmol/L) into the “desirable” range (4.9 mmol/L,  $P < 0.001$ ), and LDL also sank back into the normal range (from 3.5 to 3.3 mmol/L,  $P = 0.002$ ). Triglycerides dropped significantly from the high end of the reference range (from 2.1 to 1.5 mmol/L,  $P = 0.007$ ).

Another switch-to-abacavir study, this one randomized though small, found that substituting abacavir for d4T doesn’t improve fasting cholesterol, triglycerides, insulin, lactate, or fat mass in 24 weeks [abstract 97]. But swapping a PI or efavirenz for abacavir did improve lipids and insulin. Graeme Moyle (Chelsea and Westminster Hospital, London) found that abacavir maintained virologic control in these 30 people, all of them taking a first-line regimen including d4T and a PI or efavirenz. Everyone started with a viral load under 50 copies/mL and a cholesterol reading above 5.2 mmol/L. Moyle randomized 10 to replace d4T with abacavir, 10 to replace their PI or efavirenz with abacavir, and 10 to replace both d4T and the PI or efavirenz with abacavir and AZT.

Neither arm nor leg fat, measured by DEXA scans, changed in the d4T-to-abacavir group. Nor did any other fat or lean mass measure, or lipids, lactate, glucose, or insulin. Fat and lean mass didn’t change significantly in the other two groups. But cholesterol fell significantly in the two groups that replaced a PI or efavirenz. LDL cholesterol dropped significantly in the group who traded d4T plus a PI or efavirenz for abacavir plus AZT. That group also had a significant drop in insulin.

Another 30-person switch study failed to discern any improvements in body fat distribution among people who traded a PI for an NNRTI [abstract 83]. For 72 weeks Patrick Mallon (St. Vincent’s Hospital, Sydney) tracked 12 people with physician-diagnosed lipodystrophy who kept their PI and 18 with lipodystrophy who switched to a nonnucleoside. At the switch point the groups had similar readings for total cholesterol, HDL cholesterol, triglycerides, and glucose. The groups also reflected each other in age, time since HIV diagnosis, and duration of PI and NRTI therapy.

DEXA-measured limb fat ebbed by about 25 percent in the NNRTI group by week 48 ( $P = 0.06$ ) but rebounded toward baseline by week 72. Central fat remained stable in the switch group while edging up about 10 percent in the continued PI group, a nonsignificant change. Lean mass stayed stable in both groups, as did all lipid and glucose measures. The only significant change Mallon chalked up was a 50 CD4<sup>+</sup>-cell drop in the NNRTI group at week 48 ( $P = 0.02$ ), but T cells climbed back to baseline by week 72. Mallon con-

cluded that trading a PI for an NNRTI in these patients did nothing to improve the metabolic or morphologic abnormalities of HIV lipodystrophy.

### Atazanavir: are minuses gaining ground on pluses?

Although lipids and glucose didn’t change in Mallan’s switch study, cholesterol and insulin did improve in Moyle’s cohort, as they have in earlier looks at switching to PI-sparing regimens.<sup>21,22</sup> Moyle and Mallan’s results agree with those of earlier studies<sup>21,22</sup> demonstrating little improvement in body shape a year or more after abandoning a PI. The consistency of those morphologic findings makes the 48-week reversal of body fat abnormalities in the Trizivir study—in people who switched to Trizivir *and* in those who kept their PI—all the more mystifying (abstract 28 above).

But if switching from PIs has inconsistent effects on lipodystrophy, can *starting* with a certain PI prevent problems? A few groups studying amprenavir and the investigational PI atazanavir (BMS-232632) think the answer may be yes.

Atazanavir has one certain advantage over other PIs and one likely advantage. The first is its once-daily dosing, the second its squeaky-clean lipid profile through 48 weeks of treatment. But two 48-week trials showcased at the 8th European Conference suggest other safety problems in some people taking atazanavir—hyperbilirubinemia, lactic acidosis, and fat maldistribution. Yes, while total cholesterol, LDL cholesterol, and triglycerides stayed flat through 48 weeks of treatment with various doses of atazanavir, six people in one study and two in another suffered body fat abnormalities in that time. Two atazanavir-treated people in each study died from lactic acidosis. One of these trials coupled atazanavir with d4T and 3TC, the other with d4T and ddI.

Giuseppe Pantaleo (Vaudois University, Lausanne) laid out results of an open-label trial that compared 400 mg or 600 mg of atazanavir daily with 1,250 mg of nelfinavir twice daily in treatment-naïve people also starting d4T and 3TC [abstract O11]. (The trial was blinded only for the atazanavir dose.) Total cholesterol, LDL cholesterol, and fasting triglycerides barely budged through 48 weeks in the 181 people taking 400 mg of atazanavir or the 195 taking 600 mg. In the nelfinavir arm, total and

LDL cholesterol shot up by about 25 percent, where they plateaued through 48 weeks ( $P < 0.05$  for atazanavir versus nelfinavir by both cholesterol measures). Likewise, triglycerides lingered for 48 weeks at the baseline value in the atazanavir arms, while climbing about 50 percent in the nelfinavir group ( $P < 0.05$ ).



A four-arm 48-week comparison of atazanavir and nelfinavir plus ddI and d4T, with José Gatell (Hospital Clinic Provincial de Barcelona) atop the author list, nearly mirrored Pantaleo's lipid findings [abstract P219]. Gatell and colleagues randomized 83 people to take 200 mg of atazanavir once daily, 78 to take 400 mg, 76 to take 500 mg, and 80 to take 750 mg of nelfinavir three times daily, again in a design that blinded investigators only to the atazanavir dose.

As with other studies presented in Athens, the clinical import of these lipid differences remains unclear. Though no one can cavil at atazanavir's refreshing failure to boost lipids, one might wonder what the 25 percent cholesterol jumps in the nelfinavir arm mean. Though Pantaleo and Gatell didn't report baseline lipid numbers, one can assume investigators didn't recruit hyperlipidemic people for these studies. So the total and LDL cholesterol counts that rose 25 percent in the nelfinavir group—then plateaued there—probably made few of these patients statin candidates. The 40 to 50 percent triglyceride leaps in the two studies' nelfinavir arms may be a different story. But without baseline numbers it's impossible to say. After Pantaleo's presentation, Michael Dubé raised the point that HDL changes went unmentioned (as they did in Gatell's poster). Yet the LDL tallies reported were calculated from HDL readings, so the HDL data are sitting around somewhere.

In Gatell's study two people taking atazanavir (200 or 400 mg) quit because of lipodystrophy, one because of lactic acidosis (200 mg), and two because of hyperbilirubinemia (200 mg) or jaundice (500 mg). Grade 3 or 4 hyperbilirubinemia affected two people taking 200 mg, nine taking 400 mg, and 21 taking 500 mg, but

no one taking nelfinavir. Lactic acidosis, usually in women, racked one person taking 200 mg of atazanavir, four taking 400 mg, three taking 500 mg, and two taking nelfinavir. One person taking 400 mg of atazanavir had hepatic steatosis. Two on atazanavir and one on nelfinavir died from lactic acidosis.

In Pantaleo's study one person in each atazanavir arm quit because of high lactates, one in each arm quit because of lipodystrophy, and three taking 600 mg dropped out because of grade 4 hyperbilirubinemia. Four other people taking atazanavir also had physical signs of lipodystrophy. Two people taking 600 mg of atazanavir died from lactic acidosis.

Viral load changes were fairly consistent in the two trials. In 48-week on-treatment analyses, between 30 and 40 percent in all atazanavir and nelfinavir arms had a viral load below 50 copies/mL, not an encouraging response to any of these regimens in a treatment-naive population. In Gatell's study about 60 percent in all treatment groups had a 48-week viral load below 400 copies/mL. In Pantaleo's trial, significantly more people taking 400 or 600 mg of atazanavir than taking nelfinavir had a sub-400 viral load at 48 weeks in the on-treatment analysis ( $P < 0.05$ ). A 48-week intent-to-treat analysis showed a tighter clustering of sub-400 responders: 65 percent for 400 mg of atazanavir, 62 percent for 600 mg, and 59 percent for nelfinavir.

## Lipid and fat changes with unboosted amprenavir

A study of amprenavir, abacavir, and 3TC in 14 people naive to PIs and to those nucleosides yielded a mixed picture of metabolic and morphologic changes in 11 who completed 48 weeks of treatment [abstracts 14 and P103]. Michael Dubé (Indiana University, Indianapolis) reported steady increases in total cholesterol (perhaps offset by HDL gains) and triglycerides, some worsening glucose tolerance, and a delayed drop in insulin sensitivity that appeared to reflect fat gains. Almost everyone in the study added trunk fat, but they gained limb fat too as their lean body mass dwindled.

Dubé and coworkers enrolled 12 men and two women, including 10 Hispanics and two African Americans. Nine of 11 who reached week 48 had a viral load under 50 copies/mL (two quit after virologic failure). Fasting plasma glucose barely changed in that time, but at week 24 four people with normal glucose tolerance at baseline had drifted into the abnormal range (140 to 199 mg/dL by the two-hour oral glucose tolerance test), and two of three people with poor glucose tolerance at baseline wound up with diabetes.

Insulin sensitivity changed little through week 24, then slid, almost significantly ( $P = 0.06$ ). Because of this delayed downturn, Dubé argued that amprenavir itself didn't cause insulin resistance directly (as other PIs do), but that insulin resistance resulted from fat gains seen by week 48. That may be so, if one is willing to dismiss Haruhiko Murata's rat cell finding that amprenavir shares a fast insulin resistance mechanism with indinavir and ritonavir.<sup>3</sup> But if amprenavir caused the fat gains in Dubé's study, and if the fat gains caused insulin resistance, what is the primary cause of the insulin resistance?

Body weight and DEXA-measured total body fat rose significantly through 48 weeks (by 4.9 and 3.4 kg,  $P = 0.003$  for both), mostly reflecting gains in trunk fat (by 2.2 kg,  $P = 0.01$ ). Limb fat also inched upward (by 1.2 kg,  $P = 0.054$ ), but the trunk-to-limb fat ratio increased significantly through 48 weeks ( $P = 0.01$ ). Eight of 11 people who finished 48 weeks of treatment said they noticed more fat around the middle, and six of 11 said they saw more facial fat. Total bone mineral content also increased significantly over 48 weeks (from 2.38 to 2.42 kg,  $P = 0.02$ ).

These results seem to say that amprenavir plus abacavir and 3TC adds central fat and, to a lesser extent, peripheral fat. So 48 weeks of the regimen may yield a body shape that can be called lipodystrophic, but without the peripheral wasting often seen with other PI/NRTI combinations. Or maybe the peripheral fat wasting just hadn't started yet; in a 72-week study of people who gained central and limb fat with their first regimen, some people taking indinavir selectively lost limb fat as follow-up continued (see abstract 84 in the "HYPOTHESIS" section below). As Kathleen Mulligan observed in a workshop summary, most lipodystrophic changes happen in the second year of treatment. In that context Dubé's study is brief, and of course the sample is small.

As studies combining amprenavir with ritonavir and other PIs proliferate, and as clinicians adopt these combination tactics, it is fair to ask what useful clinical lessons can be learned from a study of standard-dose solo amprenavir. Rather, the question becomes how much amprenavir plus a PI partner will alter morphometrics.

Conveniently, Jaime Hernandez (Burnside Clinic, Columbia, South Carolina) and colleagues at three other clinics tracked 27 people who began the same regimen studied by Dubé, but then switched to 600 mg of amprenavir plus 100 mg of ritonavir twice daily [abstract 41]. Median cholesterol rose from 155 mg/dL to 191 mg/dL with amprenavir as a solo PI, then climbed only modestly after the ritonavir boost. But 40 weeks after the boost began, the median total cholesterol stood at 213 mg/dL, which means that as a group these people edged out of the "desirable" range and into the "borderline high" range (Table 2) after adding ritonavir. Only six of the 27 boosters had completed 40 weeks with amprenavir/ritonavir, so one can't make too much of this finding. But it does appear that total cholesterol keeps climbing after adding low-dose ritonavir. These variations in total cholesterol reflected increases in LDL, not HDL.

The median triglyceride value stood at 115 mg/dL at baseline and rose to 145 mg/dL with solo amprenavir. Adding ritonavir hiked the median to 180 mg/dL eight weeks after the switch ( $n = 23$ ) and to 161 mg/dL 40 weeks after the switch ( $n = 6$ ). So the median triglyceride tally stayed within the normal range (Table 2), even though ritonavir boosting continued the

inflationary trend started by amprenavir alone. Glucose concentrations did not change with amprenavir alone or amprenavir plus ritonavir.

A retrospective comparison of 143 people taking a solo PI regimen (mostly nelfinavir) and 136 taking ritonavir with another PI also spotted a few danger signals with the dual PIs [abstract 72]. Susan Hulse (University of California, Davis) charted significantly higher median triglycerides ( $P = 0.001$ ) and VLDL ( $P = 0.011$ ) in the double-PI group. The triglyceride median for the dual group measured about 210 mg/dL (versus about 170 mg/dL with one PI), and the median VLDL came in at 38 mg/dL (versus 33 mg/dL with one PI). Median total cholesterol was not significantly higher in the double PI group (190 versus 186 mg/dL). Although more people taking two PIs had a total cholesterol above 240 mg/dL (19 percent versus 12 percent taking a solo PI), that difference was not statistically significant.

A host of confounders may sway the results of both studies. Neither measured adherence or drug levels, for example, and neither mentioned diet or cotreatment with lipid lowerers. Still, mixing ritonavir with another PI appears to compound lipid problems.

### **Osteopenia links with antiretrovirals still tenuous**

The study of amprenavir, abacavir, and 3TC (abstract 14 in preceding section) is not the first to link increasing bone mineral content with PI therapy. Simon Mallal's group reported a significant positive correlation between indinavir and bone density at last year's Lipodystrophy Workshop.<sup>23</sup> That study also correlated dwindling bone density with shrinking subcutaneous fat, but indinavir's positive effect on bone proved independent of fat changes in a multivariate analysis.

At this year's workshop bone expert Pamela Robey (National Institute of Dental and Craniofacial Research, Bethesda) noted the total shutdown of fat cell formation from bone marrow stem cells in some people with congenital lipodystrophy. But this workshop made no headway in building links between fat and bone. Instead it focused on the potential roles of longer survival with HIV and of anti-HIV medicine in thinning bones. Only one study saw more bone disease in people taking PIs than in the PI naive. Giordano Madeddu

(University of Sassari, Italy) reported significantly higher rates of osteoporosis, but not osteopenia (curiously), in PI-treated people than in those taking non-PI regimens or no antiretrovirals [abstract 82].

The study evaluated 98 men and 50 women, all between 20 and 61 years old; 85 had an average 37 months of PI experience, 54 averaged 13 months with a PI-sparing regimen, and nine had no antiretroviral experience. An age- and sex-matched group of seronegative controls included 55 people. The PI group had 19 (22 percent) with WHO-defined osteoporosis, compared with 5 of 63 (8 percent) in the no-PI/no-treatment group ( $P < 0.05$ ). Rates of osteopenia were nearly identical in these two groups—35 percent for people on PIs and 36 percent for the PI naive.

Spine bone density measured by DEXA was significantly lower in the PI takers (0.92 mg/cm<sup>2</sup>) than in the non-PI treated group (0.97 mg/cm<sup>2</sup>,  $P < 0.002$ ) or the healthy controls (0.99 mg/cm<sup>2</sup>,  $P < 0.01$ ). The difference between the non-PI group and the controls was not statistically significant. Serum osteocalcin, bone alkaline phosphatase, and urinary pyridinium crosslinks all proved significantly higher in people taking PIs than in PI-naive study participants. None of these measures correlated with HIV disease progression or treatment duration in the PI group.

Three other studies reported in Athens failed to discern any ties between PIs and thinner bones, though one found more osteopenia in people taking antiretrovirals than in untreated people with HIV [abstract 32]. But the treated groups were also significantly older than the untreated people and had been infected significantly longer. Willy Rozenbaum (Rothschild Hospital, Paris) presented these results from a study of 25 treatment-naive men, 47 men taking a PI for at least 18 months, and 47 men taking a non-PI regimen for that long.

DEXA-measured osteopenia of the femoral neck affected significantly more people in the PI group (66 percent) and the non-PI group (55 percent) than in the untreated individuals (36 percent,  $P = 0.034$ ). More men taking PIs (51 percent) or PI-sparing combos (45 percent) also had osteopenia of the lumbar spine than treatment-naive people (36 percent), but that difference didn't reach statistical significance ( $P = 0.096$ ). More treated

than untreated people had trochanter osteopenia, but again the trend was not significant. Unlike Madeddu, Rozenbaum did not find more osteoporosis among PI-treated people.

One factor that favored osteopenia in the treated men was their significantly older age (40 years for the PI-treated, 43 for non-PI treated, and 37 for the naive,  $P = 0.004$ ). The treated groups had also been infected with HIV significantly longer than the untreated men ( $P < 0.001$ ) and had significantly lower current viral loads ( $P < 0.01$ ) and significantly lower CD4<sup>+</sup> nadirs ( $P < 0.01$ ). The PI and non-PI groups included significantly more men with lipodystrophy (89 and 74 percent respectively) than the treatment-naive contingent (4 percent,  $P < 0.001$ ). Significantly fewer people taking PIs (35 percent) indulged in another risk factor, smoking, than did people taking non-PI regimens (61 percent) or untreated men (56 percent,  $P = 0.033$ ).

Together, these 119 individuals with HIV infection had significantly lower bone mineral density scores for the femoral neck, trochanter, and lumbar spine than did 147 healthy men ( $P < 0.001$  for all sites). Compared with controls, the HIV group also had significantly lower weight (82 versus 71 kg) and body mass index (27 versus 23 kg/m<sup>2</sup>,  $P < 0.001$  for both), factors that typically raise the risk of osteopenia.

A study of 27 men and 8 women, most with antiretroviral experience, showed little change in bone mineral density on DEXA scans done at least one year apart [abstract P138]. Antonia Moore (Royal Free and University College Medical School, London) reported hardly any variation in median spine or femoral neck density from year to year, though total hip density slipped a fraction.

A few findings in this study indicated a bigger risk of worsening bone mineral density in people with more advanced HIV infection. All 17 people with AIDS at the first DEXA scan had worsening bone density on the follow-up scan. A univariate analysis linked higher nadir, baseline, and follow-up CD4<sup>+</sup> counts with a lower probability of worsening bone density. Only the higher follow-up CD4<sup>+</sup> count remained predictive in a multivariate analysis. The only other variable that correlated with thinning bones in a multivariate analysis was complaining about

backaches or other joint pains. About one third of these study participants had self-reported lipodystrophy. As part of this ongoing study, Moore and colleagues plan to weigh factors that may improve bone density scores, such as exercise and dietary supplements.

A study of seven men with osteopenia who underwent transiliac biopsy found no correlation between antiretroviral duration and severity of bone disease, though perhaps the small population made finding such a link unlikely [abstract 12]. Kevin Yarasheski (Washington University, St. Louis) reported that the biopsies distinguished four types of bone disease: osteomalacia in one man, high bone turnover osteoporosis in one, inactive osteoporosis in two, and normal aging osteoporosis in three. The mixed findings, he said, suggest that multiple mechanisms underlie osteoporosis in people with HIV infection. No one disagreed.

Given the still-inchoate data on bone density in HIV-infected people, the best clinical advice for now probably came in a session summary by Kathleen Mulligan: ask patients about vitamin and calcium intake, recommend weight-bearing exercise, and add osteopenia to the list of reasons to stop smoking.



If the hypothalamus lies somewhere below the thalamus, a hypothesis lies somewhere below a thesis. That posture pretty well describes the current state of the mitotoxigenicity hypothesis. But proponents of the not-yet-thesis that lipodystrophy and high lactates are mitochondrial toxicities of NRTIs are working hard to change that. They came to Athens with results of sophisticated cell studies and fat biopsies, and, at the end of the day, their case looked stronger, though hardly air-tight.

### Does less mtDNA mean less peripheral fat?

One problem in erasing the *hypo* from this hypothesis, observe Simon Mallal and coworkers, is the difficulty in setting “a ‘cut-off point’ at which the magnitude of mtDNA [mitochondrial DNA] depletion is considered pathological.”<sup>4</sup> Although

Cecilia Shikuma (University of Hawaii, Honolulu) didn’t suggest a cutoff in her PCR analysis of mtDNA in adipose tissue, she edged closer to forging a mitochondria-lipodystrophy link [abstract 20].

The PCR tool Shikuma deployed in this study improves on the semiquantitative method she used in an earlier analysis tying mtDNA depletion to lipoatrophy.<sup>24</sup> In the new study she biopsied abdominal wall fat from one person without HIV infection, five treatment-naive people with HIV, seven people without lipodystrophy after more than six months of HAART, and 10 HAART-treated people with lipodystrophy. All 10 in the lipodystrophy group had lost arm and leg fat, nine had gained abdominal fat, eight had lost facial fat, and five had larger breasts.

Copies of mtDNA per cell averaged 59 in the lipodystrophy group, 219 in the HAART group without lipodystrophy, 280 in the antiretroviral-naive people, and 1,057 in the one uninfected control. The difference between the lipodystrophy group and both the seronegative control and the naive group was statistically significant. But the difference between the HAART-treated groups with or without lipodystrophy did not reach statistical significance.

To Graeme Moyle, the nonsignificant difference between treated groups suggested that mtDNA depletion in HAART takers with lipodystrophy may be an epiphenomenon that doesn’t explain the syndrome. Shikuma agreed that her data don’t nail down mitochondrial toxicity as the cause of lipodystrophy. Indeed, in her published abstract she cautioned that “additional analysis and standardization of mtDNA analysis of tissue-specific pathology are needed to determine if mtDNA toxicity is important in HAART-associated lipodystrophy.”

A PCR study of fat cells culled from biopsies (instead of fat tissue, as in Shikuma’s study) found no significant association between lipoatrophy and mtDNA depletion in 22 people taking antiretrovirals, 13 treatment-naive individuals, and six healthy controls [abstract LB/O3]. But Simon Mallal and colleagues did find significantly less mtDNA in fat cells from 12 people taking d4T than in cells from 10 taking AZT (90 versus 389 copies/cell,  $P < 0.001$ ). Both the d4T group and the AZT group had significantly less mtDNA in fat cells than the seronegative

Figure 2. Proposed drug-induced mechanisms of lipodystrophy



Simon Mallal proposed that the rapid mitochondrial DNA (mtDNA) depletion seen with NRTIs may mirror the rapid insulin resistance seen with PIs, and that both mechanisms gradually lead to the fat abnormalities of lipodystrophy.

controls (759 copies/cell,  $P < 0.001$  for d4T and  $P < 0.023$  for AZT versus controls). The study correlated lipoatrophy with use of d4T versus AZT ( $r = 0.49$ ,  $P = 0.03$ ) and with duration of d4T therapy ( $r = 0.61$ ,  $P = 0.005$ ).

Although the d4T group averaged 20 months of AZT therapy, compared with three months of d4T in the AZT group, Mallal showed that AZT pretreatment did not affect the mtDNA results: When he looked at people treated only with AZT or only with d4T, the difference between mtDNA levels remained significant (91 copies/cell for d4T only versus 399 copies/cell for AZT only,  $P = 0.001$ ). Coadministration of ddI or 3TC with d4T did not affect d4T-associated mtDNA levels.

Copies of mtDNA dropped within months of starting d4T. Among people taking d4T for up to 50 months, mtDNA levels did not fall farther after the initial plunge and may have been creeping upward. On the other hand, in two people who switched from d4T to AZT, mtDNA levels shot from 85 to 1,230 copies/cell five months after the switch in one person and from 56 to 398 copies/cell four months after the switch in the other.

Mallal sought to fit these findings into a coherent picture by postulating that the rapid mtDNA depletion with d4T may be similar to the rapid insulin resistance with indinavir: Both mechanisms precede, and could lead to, the physical changes of lipodystrophy (Figure 2). That may explain why the fast mtDNA depletion didn't correlate with lipoatrophy in Mallal's analysis.

"The main message that we've derived from the lack of correlation between mtDNA depletion and presence of lipoat-

rophy," Mallal wrote to *IAPAC Monthly*, "is that these processes don't occur over the same time frame. Within the d4T group, it may be that the major determinant of fat wasting is not so much *how low the mtDNA goes* (as it is markedly depleted) but *how long very low levels of mtDNA are maintained*."

Even though mtDNA levels didn't correlate statistically with lipoatrophy in Mallal's analysis, nine of 12 d4T takers had clinical lipoatrophy, compared with four of 10 on AZT, two of whom had switched from d4T to AZT. Neither did lipoatrophy correlate with age, percentage of CD4 cells, or duration of other NRTIs or PIs.

As logical as Mallal's hypothesis may sound, it must be tested in the clinical crucible, where logic sometimes falters. For example, a 72-week follow-up of treatment-naïve people starting their first HAART regimen found no more atrophy in d4T-treated people than in those taking AZT [abstract 84]. Patrick Mallon kept track of fat changes with DEXA scans in 35 people. Equivalent proportions began with d4T/3TC, ddI/d4T, or AZT/3TC plus a PI or an NNRTI. Mallon grouped people into those who gained central and limb fat, those who gained central and limb fat then selectively lost the limb fat, and those who didn't fit into either category.

The 72-week intent-to-treat analysis showed that exactly the same proportion in each NRTI subset fell into the gain-only group (29 percent) and that exactly the same proportion in each NRTI subset fell into the gain-then-loss group (27 percent). More people starting with indinavir than with nelfinavir or saquinavir fit the gain-then-loss profile, but Mallon rated the association "weak."

Mallal didn't feel these findings unhinge his hypothesis, pointing out that "it is always difficult to assess the significance of negative results (ie, no difference between the groups considered) in studies involving small numbers, especially when data is further divided," as in Mallon's study. Yet Mallon's results confirm once more that sorting through drug-specific toxicities is no tidy undertaking. In a straightforward human hepatoma cell system, for example, Ulrich Walker (University Clinic, Freiburg) documented a neat hierarchy of mitochondrial depletion for NRTIs, with little-used zalcitabine (ddC) the worst offender [abstract 18]:

$$\text{ddC} > \text{ddI} > \text{d4T} > \text{AZT} = 3\text{TC}$$

(What about abacavir? Walker said Glaxo declined to provide drug for his study.) Yet, if this hierarchy is correct, and if lipoatrophy is a mitochondrial toxicity, one would expect Mallon's study to show the most atrophy with ddI/d4T, followed by d4T/3TC, then by AZT/3TC. But that didn't happen. Did something go amiss somewhere between the hepatoma cells, the mitochondrial hypothesis, and Mallon's clinic?

Maybe the solution to this conundrum lies deeper in Walker's crafty little study. He did much more than size up the mitochondria-depleting potential of single nucleosides; he also studied NRTIs in combination, and he studied their effect on cell growth, lactate production, intracellular lipid droplets, and the mtDNA-encoded respiratory chain subunit COX II. It turns out that the combinations AZT/3TC, d4T/3TC, and ddC/d4T all churned up more of these toxicities together than the individual components did alone. But under these experimental conditions, ddI/d4T was not more toxic than ddI alone.

Walker also showed that mtDNA depletion is not the driving force behind all these other cellular insults, at least not with all the NRTI duos studied. AZT/3TC "behaved peculiarly," he found, "in increasing lactate and cell death independent of a decline of mtDNA and without dramatically augmenting cellular lipids."

A possible shortcoming in Walker's system, one attendee observed, is its reliance on a constant drug level, whereas drug concentrations wax and wane in human cells.

Walker concurred with this comment, noting that no cell study will ever mimic what happens under a human's skin. But he argued that such results can enlighten clinical studies. Simon Mallal and David Nolan make the same point in their review of the workshop. "Investigating the temporal relationship between introduction of NRTI therapy and mitochondrial depletion," they write, "now becomes a research priority."<sup>1</sup>

A clinical study that didn't measure mitochondrial retreats, but did measure peripheral fat in people stopping d4T or AZT, suggested that lost arm and leg fat may return. But ever so slowly. About a month before the workshop Andrew Carr reported early results of the MITOX study, which randomized 105 people with lipoatrophy to continue taking regimens containing AZT or d4T, or to replace those drugs with abacavir.<sup>25</sup> Most MITOX participants, 80 percent, were on d4T.

Six months after the switch, DEXA scans described a small but significant 10 percent gain in subcutaneous fat among the switchers. Neither clinicians nor study participants saw what the DEXA scans saw, but they will if the gains continue. Even that happy denouement may leave the *hypo* on the front end of the MITOX hypothesis, since the trial didn't call for mtDNA measurements.

### Most lactate studies point to the d-drugs

In some studies, like the hepatoma cell experiments of Ulrich Walker (abstract 18 in the preceding section), ddI outdoes d4T in evicting mtDNA. In Simon Mallal's human fat cell study, on the other hand, d4T ranks as prime banisher of mtDNA (abstract LB/O3 above). The two d-nucleosides also compete in launching lactates to higher levels, as several recent studies and workshop presentations show.

Just after the workshop, the Swiss HIV Cohort Study team found that people taking d4T—with or without ddI—had a 2.7 times higher risk of high lactates (more than 1.1 times the upper limit of normal) than people taking AZT.<sup>26</sup> And the risk kept climbing as time on d4T grew. The authors wrote that "the association between hyperlactatemia and [d4T] with or without [ddI] was not biased by these medications being more recently available and, therefore, being given preferentially to patients who had prolonged use of nucleoside[s]."

Overall, 8.3 percent of the 880-person cohort had hyperlactatemia by the definition used, and 1 percent had moderate or severe elevations, defined as more than 2.2 times the upper limit of normal. The high lactates correlated with lipoatrophy, hyperlipidemia, and hyperglycemia.

In a larger chunk of the Swiss HIV Cohort, some of the same investigators cited both ddI and d4T for lactate elevations.<sup>27</sup> This cross-sectional study done from August through September 1999 checked for a laundry list of drug side effects and bad lab readings in 1,160 people. Then the Swiss correlated those drug-endowed ravages with the antiretrovirals being taken. The analysis excluded people who switched drugs within the past 30 days, and the Swiss team tried to compensate for the effects of earlier regimens on long-term side effects by including duration of earlier antiretrovirals as a covariable in their model. They linked only two drugs to a higher risk of high lactates: d4T upped the odds 1.7 times, and ddI 1.8 times. Only two drugs, neither of them PIs, could be linked to lipodystrophy, as originally defined by Carr<sup>28</sup>: d4T and 3TC.

At the workshop a smaller cohort study fingered d4T as the prime culprit in severe hyperlactatemia (5 mmol/L or more) [abstract 65]. Yann Gérard and coworkers in Tourcoing, France, prospectively measured high lactates (at least two lactates at or above 2 mmol/L, at rest) in 59 of 866 people with HIV infection, for a calculated incidence of 20 per 1,000 person-years among treated people. Eight of nine people with severely elevated lactates were taking d4T. These were not heavily treated people; the median antiretroviral duration in this subgroup measured just nine months.

A retrospective review of symptomatic hyperlactatemia in the Frankfurt HIV Cohort also found d4T in the biggest share of offending regimens [abstract 36]. But ddI ran almost neck-and-neck with d4T in this contest. Markus Bickel (J.W. Goethe University Clinic, Frankfurt) counted 12 women and eight men with lactates above 2.4 mmol/L (median 5.94 mmol/L at diagnosis) plus symptoms such as fatigue, exercise intolerance, persistent nausea or vomiting, and abdominal pain. Of these 20, 18 were taking d4T, 15 ddI, 13 3TC, 10 abacavir, and two AZT. But the precise impact of current nucleosides was hard to gauge because these people averaged 46 months of antiretroviral treatment (range

eight to 87 months).

The correlation between high lactates, lipoatrophy, hyperlipidemia, and hyperglycemia in the Swiss HIV Cohort Study<sup>26</sup> suggests that hyperlactatemia may figure in manifestations of the lipodystrophy syndrome. Ove Andersen (Hvidovre University Hospital, Copenhagen) pursued that tangent in a case-control study of 17 HAART-treated men with lipodystrophy and 16 men taking HAART but without lipodystrophy [abstract 9].

Fasting lactates proved significantly higher in the lipodystrophy group (1.62 versus 1.37 mmol/L,  $P < 0.05$ ). But levels were normal in both groups except for one man with lipodystrophy and a lactate of 4.4 mmol/L who was excluded from the foregoing comparison. The lipodystrophy group also had significantly impaired glucose disposal compared with the controls (5.5 versus 8.0 mg/min/kg lean body mass,  $P = 0.003$ ). Although serum lactate correlated inversely with glucose disposal in controls, Andersen did not find that inverse correlation in the men with lipodystrophy. That contrast led him to suggest that men with lipodystrophy metabolize lactates differently from HAART-treated men without lipodystrophy. In her workshop summary, Kathleen Mulligan credited Andersen's speculation. But she noted that the story may differ in people with high lactates.

Andersen found no correlation between lactate levels and duration of NRTI therapy, or between lactates and d4T or AZT. But again those findings could change if lactates climbed into the danger zone.

### Another look at lactate screening

One group of clinicians tried to do something about high lactates and the symptoms they sometimes cause. In 16 people with lactates above 2.2 mmol/L, T. Lonergan (University of California, San Diego) and colleagues replaced d4T with either AZT or abacavir [abstract 81]. Everyone had taken d4T for at least six months and had a viral load under 400 copies/mL. Ten of those 16 stopped antiretrovirals completely before resuming with an AZT or abacavir regimen.

Twelve weeks after starting an AZT or abacavir combo, the median lactate had fallen from just under 3.0 mmol/L to just above 1.5 mmol/L. Abdominal pain or bloating improved 12 weeks after the switch in four of the 16, stayed the same in 11, and got worse in one. A few people said nausea,

vomiting, or loss of appetite improved after the switch. But those symptoms worsened in a few others and stayed the same in everyone else. Liver enzymes fell substantially in people who replaced d4T with abacavir or AZT.

Loneragan also replaced d4T with AZT or abacavir in 106 people with lipoatrophy and lactates under 2.2 mmol/L. Like the group with high lactates, these people had viral loads under 400 copies/mL and had taken d4T for at least a half year. Their median lactate eased by a mere 0.1 mmol/L 12 weeks after the switch. (That result mirrored the average drop from 1.5 to 1.4 mmol/L in Graeme Moyle's 24-week d4T-to-abacavir switch study; see "Can abacavir avert or reverse lipodystrophy?" above.) Among people in Lonergan's cohort with lactate-linked symptoms but levels under 2.2 mmol/L, equally small proportions felt the symptoms got better or worse after stopping d4T, while most said things stayed the same. Lonergan saw no change in lipoatrophy, which one wouldn't expect to improve in 12 weeks. So stopping d4T in this group doesn't do much, at least not in three months.

The question raised, and usually unanswered, by lactate studies is whether routine clinical screening will help prevent dangerous elevations. Lonergan proposed that, "although routine testing of lactate levels is not generally recommended . . . it is useful for patients with unexplained symptoms or elevated [liver function test] abnormalities." He urged clinicians to quiz such patients about symptoms that may signal inflated lactates. The Swiss investigators take an even more aggressive stance, writing that "determination of lactate levels may prove useful in the screening for mitochondrial toxicity."<sup>26</sup>

But anyone pondering lactate screening should first pour through the results of another study by Graeme Moyle, this one involving 4,391 lactate samples from 2,069 people, 1,239 of whom had taken antiretrovirals for at least four months [abstract 98]. This study had two intriguing features. First, its size allowed Moyle to analyze a substantial subset of 312 people still taking their first nucleoside combination, a strategy that eliminates potential bias from previous regimens. Second, Moyle read lactates at least twice in 750 people to reckon how much a first level influences a second. Using his laboratory's standard, he called anything above 2.5 mmol/L an elevation.

Among the 312 people still on their

first NRTIs, 11 of 71 (15.5 percent) taking ddI had a high lactate, compared with 14 of 241 (6 percent) taking 3TC plus either d4T or AZT. Rates for d4T and AZT didn't differ when those nukes were combined with either 3TC or ddI. A univariate analysis of these numbers didn't tie ddI, or any demographic or disease factor, to a higher risk of lofty lactates. But analysis of the entire treated population found a significantly lower risk of lactate elevations among people taking d4T/3TC or 3TC/abacavir than among those taking ddI/d4T. And 67 percent of people with severe acidemia (above 5 mmol/L) were taking ddI/d4T.

The question, then, becomes how worried to get about a lactate somewhere above the normal range but still not "severe" or breeding symptoms. In Moyle's longitudinal analysis, a lactate below 2.5 mmol/L almost always meant the next value would be in that range (positive predictive value 94 percent). For people with one reading above 2.5 mmol/L, the next reading usually fell into the normal range (positive predictive value 39 percent).

Moyle concluded that a single lactate sample during antiretroviral therapy "may be used to screen for those individuals who may require additional observation." In a less formal appraisal of this massive lactate toting, he suggested that "lactate screening has produced more neurosis for us than clinical benefit." In the same Q&A session, Simon Mallal noted the near impossibility of finding predictors of acidosis, because it's such a rare event. And in the workshop summary he penned with David Nolan, Mallal proposed that chronically elevated lactates lingering below 3 mmol/L may "represent a 'compensated' form of hyperlactatemia, in which homeostasis of lactate metabolism has been achieved."<sup>1</sup> If that's true, drug switching simply to lower such lactates would seem ill advised.



## MIMESIS (FIXING FACIAL ATROPHY)

*Mimesis* is a sturdy word that doesn't get tossed around much anymore, though mimes and mimics would be unnamed without it. For physicians *mimesis* means the hysterical simulacrum of an organic disease. But for the arts-and-letters crowd, it just means imitating nature. People with HIV lipodystrophy may be this decade's keenest students of that kind of mimesis.

And the nature they want to mime is the body or face they had before starting antiretrovirals. A survey by Emmaneul Trenado (AIDES, Pantin, France) found that 87 percent of 173 people with facial atrophy want an implant to fix it [abstract 122]. But most haven't gone ahead because they lack information or the money for implants.

A handful of studies shows that at least a few clinicians are avidly pursuing mimetic remedies for people with lipodystrophy. Marcio Serra (CTA-AIDS, Rio de Janeiro) injected solutions of phosphatidylcholine (4 cm<sup>3</sup>) and mesocaine (1 cm<sup>3</sup>) every two to three weeks in the backs and necks of two men with painful fat pads [abstract 115]. Both men had pain relief and improved movement after the third injection and a marked reduction in pad size after the sixth. For 120 people with facial atrophy, Serra implanted polymethylmethacrylate in a 30 percent solution that included hydroxyethylcellulose and lidocaine [abstract 114]. After at least 12 months of follow-up, all of these people claimed to be satisfied with the results, though Serra noted that some needed additional injections in the same or new areas after 12 months.

A one-year study of polyvinyl gel microspheres for severe facial atrophy found that 33 of 35 people (23 men and 12 women) rated the results excellent or very good [abstract 50]. Santiago Moreno (Ramón y Cajal Hospital, Madrid) reported that two thirds of these people needed only two surgery sessions, less than the four or five typically needed with other lipoatrophy implant procedures. Moreno and coworkers have now treated 160 people with the microspheres.

Probably the best studied implant technique for facial atrophy involves Newfill, a synthetic polymer of polylactic acid (PLA). Parisian surgeon Patrick Amard reported good results with this biodegradable, bioabsorbable substance at last year's Lipodystrophy Workshop<sup>29</sup> and again at the Cannes lipodystrophy meeting earlier in 2001.<sup>30</sup> The European Conference in Athens featured a 50-person study of Newfill with six months of follow-up [abstract O20].

Camille Aubron-Olivier told attendees that four people have had three sets of injections (one in each cheek), 29 had four, and 17 had five. Ultrasound-measured total cutaneous thickness, which includes adipose and dermal tissue, surged from a median 2.9 mm at baseline to 8.1 mm at

month two and 9.5 at month six. All study participants professed satisfaction with the six-month results, and no serious side effects emerged. Five people had palpable but invisible subcutaneous nodes near the injection sites, but the nodes appeared to be shrinking. Nearly everyone experienced some edema after each procedure, but it always resolved in 24 to 48 hours. Among 13 people monitored for at least 12 months, none needed further injections.

In Trenado's survey, 28 of 38 responders who had a facial implant for atrophy used Newfill, which is licensed in France. Clinicians in the UK have been studying the product, but some sites are having a hard time getting surgeons to set aside a few hours from their lucrative tummy-tuck trades. At least six sites in the US and Mexico began Newfill programs with per-session prices ranging from US\$500 to US\$650.<sup>31</sup> Aubron-Olivier said the tab in France comes to 300 Euros, or about US\$270. But at this writing, unless people in the Americas can also pay for periodic jaunts to Mexico, they'll have to wait to try Newfill. The FDA put at least a temporary halt on importing the product for research.

In Western culture the mimetic arts got their start in Greece, when Thespis took two steps out of the chorus and invented dialogue, and when Archaic sculptors made bold to mime the human form in beguiling statues of naked young men—kouroi—and draped young women—korai. Workshop attendees who found their way to the National Archaeological Museum saw room after room of kouroi and korai, each smiling that same enigmatic Attic smile.

Why? A placard in the museum suggests that the kouros, "with his heroic nudity . . . epitomizes perpetual youthfulness, eternal beauty, the power, hope and bliss of life." Such thoughts would make most of us break into a toothy grin, but the wan Archaic smile suggests something else. Perhaps the kouros, at least, is hiding a little joke from the passing voyeur. Though each statue may represent an actual man, that man's body probably never looked as svelte as the idealized youth depicted. In fact, many a kouros was probably fat, old, and dead when someone sliced his imagined shape from Pentelic marble. Maybe that famously cryptic smile is a last, bitter laugh at anyone gullied into thinking he ever had such rippling arms and legs, and such a flat belly.

Whether people with HIV lipodystrophy will get the last laugh at their antagonists—HIV and the drugs that treat it—is a tough call. But this meeting gave some hope that the laugh won't be bitter. One can see that already in Marcio Serra's before-and-after photos of men and women with facial atrophy. Some are smiling after *and* before their implant course, perhaps hoping for the best. And there is nothing enigmatic about the smiles, or the procedure's results.

The workshop also saw a shift toward more evidence-based therapy for accumulating fat, with treatments that address newly appreciated mechanisms. Understanding those mechanisms may help fashion anti-retrovirals that don't cause so many problems in the first place. But drug making has probably grown too sophisticated to profit from lessons taught by that other Greek mimetic art, drama. The Prometheus of Aeschylus not only gives humans fire; he also shows them how to make medicines that cure all ills "by the blendings of mild simples."<sup>32</sup> ■

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

## References and Notes

- Mallal S, Nolan D. Therapy for life: understanding and managing long-term antiretroviral toxicity. Handout at GlaxoSmithKline symposium. 8th European Conference on Clinical Aspects and Treatment of HIV Infection. October 23-31, 2001. Athens.
- Noor MA, Lo JC, Mulligan K, et al. Metabolic effects of indinavir in healthy HIV-seronegative men. *AIDS* 2001;15:F11-F18.
- Murata H, Hruz PW, Mueckler M. The mechanism of insulin resistance caused by HIV protease inhibitor therapy. *J Biol Chem* 2000;275:20251-20254.
- Nolan D, John M, Mallal S. Antiretroviral therapy and the lipodystrophy syndrome, part 2: concept and aetiopathogenesis. *Antiviral Ther* 2001;6:145-160.
- Tsioufas S, Mantzoros C, Hammer S, Samore M. Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and lipodystrophy. *Arch Intern Med* 2000;160:2050-2056.
- Luna B, Feinglos MN. Drug-induced hyperglycemia. *JAMA* 2001;286:1945-1948. Citing the American Diabetes Association, the authors list the following risk factors for hyperglycemia: (1) impaired glucose tolerance (fasting plasma glucose  $\geq 110$  mg/dL [ $\geq 6.1$  mmol/L] but  $< 126$  mg/dL [ $< 7.0$  mmol/L]), (2) a family history of hyperglycemia, (3) being a member of a high-risk population, including African Americans, Hispanic Americans, Native Americans, Asian Americans, and Pacific Islanders, (4) obesity ( $\geq 20$  percent above desired body weight or body mass index  $\geq 27$  kg/m<sup>2</sup>), (5) "habitual physical inactivity," (6) blood pressure  $\geq 140/90$  mm Hg, (7) HDL cholesterol  $\leq 35$  mg/dL ( $\leq 0.91$  mmol/L) and/or triglycerides  $\geq 250$  mg/dL ( $\geq 2.8$  mmol/L), (8) a history of gestational diabetes mellitus or delivery of a baby weighing  $> 4$  kg, (9) polycystic ovary syndrome.
- Slom T, Weverling G, Katlama C, et al. Body composition changes in HIV-infected patients treated with NRTI, non-NRTI, or PI-based therapy: preliminary results of the fat redistribution and metabolic substudy (FRAMS) of the Atlantic study. 1st IAS Conference on HIV Pathogenesis and Treatment. July 8-11, 2001. Buenos Aires. Abstract 488.
- Balanchine G, Mason F. *101 Stories of the Great Ballets*. Garden City: Doubleday. 1975:2.
- Walli R, Michl GM, Muhlhaber D, et al. Effect of troglitazone on

- insulin sensitivity in HIV-infected patients with protease inhibitor-associated diabetes mellitus. *Res Exp Med* 2000;199:253-262.
- Arioglu E, Duncan-Morin J, Sebring N, et al. Efficacy and safety of troglitazone in the treatment of lipodystrophy syndromes. *Ann Intern Med* 2000;133:263-274.
- Hadigan C, Corcoran C, Basgoz N, et al. Metformin in the treatment of HIV lipodystrophy syndrome: a randomized controlled trial. *JAMA* 2000;284:472-477.
- Hadigan C, Meigs JB, Rabe J, et al. Increased PAI-1 and tPA antigen levels are reduced with metformin therapy in HIV-infected patients with fat redistribution and insulin resistance. *J Clin Endocrinol Metab* 2001;86:939-943.
- Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-2497. Online at <http://jama.ama-assn.org/issues/v285n19/pt2/jsc10094.pdf>. Accessed November 29, 2001.
- Moyle GJ, Lloyd M, Reynolds B, et al. Dietary advice with or without pravastatin for the management of hypercholesterolemia associated with protease inhibitor therapy. *AIDS* 2001;15:1503-1508.
- The Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-1357.
- Powderly WG. Metabolic complications and adverse drug reactions in HIV. Medscape HIV/AIDS. Online at <http://hiv.medscape.com/44989.rhtml>. Accessed November 19, 2001.
- Lucas GM, Chaisson RE, Moore RD. Comparison of initial combination antiretroviral therapy with a single protease inhibitor, zidovudine and zalcitabine, or efavirenz. *AIDS* 2001;15:1679-1686.
- Sabin C, Matthews G, Mandala S, et al. A comparison of initial treatment regimens in ARV-naïve patients starting HAART. 1st IAS Conference on HIV Pathogenesis and Treatment. July 8-11, 2001. Buenos Aires. Abstract 241.
- Tashima K, Staszewski S, Morales-Ramirez J, et al. 3-year durability of response with an efavirenz (EFV)-containing regimen: 144-week follow-up of study 006. 1st IAS Conference on HIV Pathogenesis and Treatment. July 8-11, 2001. Buenos Aires. Abstract 224.
- Holmberg S, Moorman AC, Tong T, et al. Protease inhibitor drug use and myocardial infarction in ambulatory HIV-infected patients. 39th Annual Meeting of the Infectious Diseases Society of America. October 25-28, 2001. San Francisco. Abstract 941.
- Martinez E, Conget I, Lozano L, et al. Reversion of metabolic abnormalities after switching from HIV-1 protease inhibitors to nevirapine. *AIDS* 1999;13:805-810.
- Ruiz L, Negro E, Domingo P, et al. Antiretroviral treatment simplification with nevirapine in protease inhibitor-experienced patients with HIV-associated lipodystrophy: 1-year prospective follow-up of a multicenter, randomized, controlled study. *J AIDS* 2001;27:229-236.
- Nolan D, Upton R, McKinnon E, et al. Stable or increasing bone mineral density in HIV-infected patients treated with nelfinavir or indinavir. *AIDS* 2001;15:1275-1280.
- Shikuma CM, Hu N, Milne C, et al. Mitochondrial DNA decrease in subcutaneous adipose tissue of HIV-infected individuals with peripheral lipodystrophy. *AIDS* 2001;15:1801-1809.
- Carr A et al. Switching d4T or AZT to abacavir (ABC) for HIV lipodystrophy: a randomised, controlled, open-label, multicentre, 24-week study. 13th Annual Conference of the Australasian Society for HIV Medicine. October 4-7, 2001. Melbourne. Abstract 148.
- Boubaker K, Flepp M, Sudre P, et al. Hyperlactatemia and antiretroviral therapy: the Swiss HIV Cohort study. *Clin Infect Dis* 2001;33:1931-1937.
- Fellay J, Boubaker K, Ledergerber B, et al. Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study. *Lancet* 2001;358:1322-1327.
- Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS* 1998;12:F51-F58.
- Amard P, Saint-Marc T, Katz P. The effects of polyolactic acid as therapy for lipodystrophy of the face. *Antiviral Ther* 2000;5(suppl 5):79.
- Amard P. Role of plastic surgery in treatment of fat wasting and fat accumulation. 2nd European Workshop on Lipodystrophy. April 19-21, 2001. Cannes. Abstract O-24.
- Berger DS. New facial filling treatment for lipodystrophy. *Positively Aware* Sep/Oct 2001. Online at [http://www.thebody.com/tpan/sep/oct\\_01/new\\_fill.html](http://www.thebody.com/tpan/sep/oct_01/new_fill.html). Accessed December 3, 2001.
- Kott J. *The Eating of the Gods*. Evanston, Illinois: Northwestern University Press. 1987:17.



## SAY ANYTHING



Access to antiretrovirals is maybe a utopia but it is a necessary one. Don't start an ideological battle here. The antiretrovirals are an element of competence against AIDS, let us try and get them for free.

*Aliou Sylla, a Mali physician, quoted in a December 10, 2001, Agence France Presse article entitled, "Access to Better Treatment Dominates African AIDS Conference." Access to antiretroviral drug therapies dominated talks at the 12th International Conference on AIDS and Sexually Transmitted Diseases in Africa held December 9-13, 2001, in Ouagadougou, Burkina Faso. At the conference's opening session, UNAIDS representatives predicted that in the absence of proper treatment, most HIV-positive Africans are not expected to survive the present decade.*



In sub-Saharan Africa, 28.1 million people have HIV, 55 percent of whom are women. In no other continent on the world is the number of infected women so preponderant. The irony is that women are considered by men to be vectors of the virus. It is the other way around. They are victims.

*Marie-Louise Ndala Musuamba, President of the Court of Appeal in the Democratic Republic of the Congo's capital, Kinshasa, was among women delegates at the 12th International Conference on AIDS and Sexually Transmitted Diseases in Africa in Ouagadougou, Burkina Faso, who lashed out at the male-dominated culture in Africa, saying that men pose an incredible risk to women in terms of spreading HIV. Musuamba said women in Africa are frequently forced to be subservient to men, are not afforded the same opportunities in education and employment, and are often regarded as little more than chattel.*



The campaign for antiretroviral treatment in the third world is no longer a battle of ideas; this year the world recognized that universal treatment is both imperative and feasible. What is left is the struggle for money. Until that is won, AIDS will remain treatable for the poor in theory alone.

*Tina Rosenberg, author of a December 9, 2001, New York Times editorial entitled, "Global Antiretroviralism," believes that small pilot projects conducted in resource-limited clinics in poor nations have found inexpensive ways to treat people successfully, "even in the most remote and miserable places." She argues that these experiences demonstrate that the cost of scaling up antiretroviral drug access rather than the lack of capacity to deliver antiretroviral drug therapies remains the issue.*



We weren't allowed in, so we just stood there shouting. We screamed: "People are dying and you do nothing but detain them," and "What sort of officials are you?"

*Xie Yan, 35, a mother of three whose husband died earlier this year and who has been told she will be dead in two years, quoted in a December 12, 2001, New York Times article. According to the article entitled, "Spread of AIDS in Rural China Ignites Protests," as China's central government takes belated steps to address that country's growing AIDS crisis, continuing suppression of protesting villagers with HIV is becoming increasingly difficult. In late November 2001, as China marked its first World AIDS Day in Beijing, officials in Suixian County detained poor farmers wasting away from AIDS, as well as Chinese journalists who had come to interview them.*



The old problems that existed on September 10, [2001], before the attack, are still with us: the elimination of poverty, the fight against HIV/AIDS, the question of the environment... We need to think of the future and the planet we are going to leave our children and their children.

*From United Nations Secretary-General Kofi Annan's 2001 Nobel Peace Prize lecture delivered December 11, 2001, in Stockholm. The Nobel Peace Prize was jointly awarded in 2001 to Annan and the United Nations in recognition of their promotion of peace and championing of individual rights in an unstable and unequal world. Annan stated the Nobel Peace Prize monetary award of US\$947,000 will benefit a single United Nations project.*



[The United States has a] responsibility to lead the world in confronting one of the most compelling humanitarian and moral challenges facing us today.

*Henry Hyde, Chairman of the US House of Representatives' International Relations Committee, quoted in a December 12, 2001, Associated Press report about US House of Representatives approval that day of a US\$1.3 billion appropriation with which to combat HIV/AIDS worldwide, effectively doubling the amount budgeted in the 2001 fiscal year's foreign aid bill. According to the Associated Press, the legislation would assign US\$750 million for an international AIDS trust fund and US\$485 million in bilateral aid to be spent on education, as well as treatment and prevention programs through nongovernmental organizations. The legislation would also approve the spending of US\$50 million for a pilot program to assist developing countries in acquiring antiretroviral drugs and other pharmaceutical supplies.*