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IAPAC

MONTHLY



FEATURE: IAPAC Celebrates 10 Years

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Happy birthday, IAPAC!

José M. Zuniga

The International Association of Physicians in AIDS Care (IAPAC) was incorporated February 7, 1995, to marshal the strength of physicians and allied health professionals in an effort to improve the quality of care provided to men, women, and children living with HIV/AIDS. Ten years later, IAPAC President/CEO José M. Zuniga reminisces about the past and forecasts the future.



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“...At a profound, even instinctual, level—because it precedes rational analysis—people become physicians to struggle against the weight of human suffering, and thereby place themselves squarely on the side of those who intervene in the present, because they believe the future can be different.”

—Jonathan Mann



REPORT FROM THE PRESIDENT

A decade ends, another begins

José M. Zuniga

My partner and I recently celebrated our 10-year anniversary. Leading up to this personal milestone, I thought a great deal about what brought us together, the challenges we have overcome, the experiences we have shared, and the prospect of our future. So, too, as I preside over the International Association of Physicians in AIDS Care (IAPAC) 10 years after its incorporation, I find myself contemplating our association's genesis, our accomplishments, and the challenges that lie ahead as we advance our mission to improve the quality of care provided to men, women, and children living with HIV/AIDS.

For two years after its incorporation in February 1995, IAPAC focused much of its attention on the US AIDS epidemic. This was important given the coinciding advent of antiretroviral therapy and the critical need to keep physicians abreast of developments as one after another anti-retroviral drug was approved by the US Food and Drug Administration (FDA), offering HIV-positive patients myriad treatment options, extending their lives, and improving their quality of life.

I joined IAPAC in August 1997 and my immediate task was to plan and host our 1st International Conference on Healthcare Resource Allocation for HIV/AIDS in Washington, DC. I was honored to work with the late Jonathan Mann (one of IAPAC's founding physician members) to develop one of the first programs that, by way of demanding recognition of HIV/AIDS care as a human right, advocated the need for strategic thinking around the foresight that the increasingly "miraculous" antiretroviral drugs producing a Lazarus-like effect in the resource-rich North must become available in the



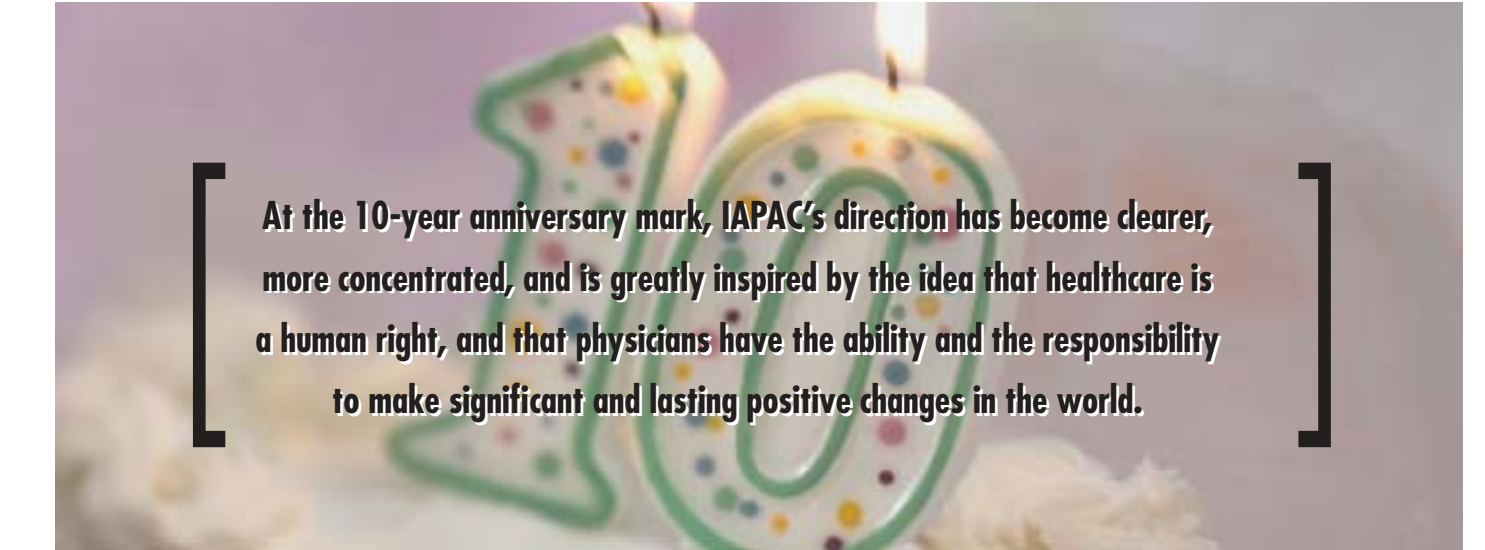
resource-impooverished South. We did so by featuring panel discussions involving all actors—including pharmaceutical companies—and proposing a re-doubling of efforts to expand access to antiretroviral therapy in the developing world (an unpopular concept at that time).

Our goal was to stir an international health bureaucracy to act against an AIDS epidemic of global proportions. In a memorable keynote address, Jonathan challenged delegates by stating that, "to become a physician implicitly places us on the side of those who believe that the world can change. Every act challenges the apparent inevitability of the world as it is and the natural history of illness, disability, and death... At a profound, even instinctual, level—because it precedes rational analysis—people become physicians to struggle against the weight of human suffering, and thereby place themselves squarely on the side of those who intervene

in the present, because they believe the future can be different."

Over the course of the past eight years, and in line with Jonathan's challenge, IAPAC has significantly expanded its programs as well as its geographical reach, in an effort to represent and assist physicians and allied healthcare professionals as they combat HIV/AIDS and its associated scourges in all corners of the world. Through myriad advocacy, medical and patient education, and technical assistance initiatives spearheaded by physician members and implemented by a dedicated international staff (through whom our vision is made reality), IAPAC has made a tangible impact on the delivery of HIV/AIDS care.

- **Globally.** IAPAC has published a monthly newsjournal (*IAPAC Monthly*) and quarterly clinical journal (*JIAPAC*), hosted six International Conferences on Healthcare Resource Allocation, influenced public policy at various levels (eg, World Health Organization [WHO]), and advanced Jonathan's human rights legacy. In addition, IAPAC has engaged in strategic partnerships with numerous institutions (eg, American International Health Alliance [AIHA]) to deliver Global AIDS Learning & Evaluation Network (GALEN) trainings in various countries, including China, Honduras, and the Ukraine.
- **United States and Western Europe.** IAPAC has distributed tens of thousands of publications meant to facilitate the safe and optimal use of antiretroviral therapy, hosted five clinical symposia (IAPAC Sessions), and participated in the development of public policy measures meant to improve the quality of care provided to people living with HIV/AIDS.
- **Africa.** IAPAC has trained more than 13,000 healthcare professionals on the management of opportunistic infections



At the 10-year anniversary mark, IAPAC's direction has become clearer, more concentrated, and is greatly inspired by the idea that healthcare is a human right, and that physicians have the ability and the responsibility to make significant and lasting positive changes in the world.

through the Diflucan Partnership Program (DPP). And, throughout sub-Saharan Africa, IAPAC has either directly trained or collaborated in the training of thousands of physicians using the GALEN curriculum.

Where are we heading? Our future is defined by five fundamental objectives:

- **Effecting sustainable change.** Any number of short-term efforts have come and gone in the most AIDS-ravaged countries on the planet, contributing to a hodge-podge of activities that too often have limited (or temporary) impact. IAPAC aims not to create temporary schemes but is planning for and aiming toward long-term, macro solutions that, in the long run, will change not just HIV/AIDS care, but will help to transform the delivery of healthcare services in general to a level more consistent with the principle of healthcare as a human right.
- **Partnering for better health.** IAPAC will continue to partner with like-minded individuals, institutions, corporations, and governments to combine efforts, pool resources, and thus create a more stable, sustainable environment for the provision of healthcare. IAPAC alone cannot create or sustain the type of symbiosis that is only acquired by combining strengths with others.
- **Volunteering for a better future.** IAPAC is fortunate to count on a great reservoir of talented and dedicated volunteers from which to draw to advance our various activities. Harnessing the power of these volunteers will be essential for creating

the type of large-scale change that is necessary. I will keep you apprised of the many opportunities for volunteering your skills and energy that will be forthcoming in the next few months.

- **Providing fundamental resources.** IAPAC is committed to creating programs that will prove to be essential in the provision of healthcare services, with special emphasis on the delivery of safe and optimal antiretroviral therapy. We are exploring all avenues of communication, including print, virtual, radio, and television to disseminate these resources to those who need them most.
- **Building a platform for growth.** The idea of building upon our foundations is integral to IAPAC's strategic planning. Every decision will continue to be made based on the building blocks approach that has fostered our association's growth over the past 10 years.

I will expand on each of these objectives over the course of the next several months. Suffice it to say that IAPAC is poised for incredible growth in the very near future as a result of sustained investment by our membership, as well as in response to increased need for the expertise and dedication embodied by our membership. I expect to have several major announcements in the near future regarding new programs and opportunities, each of which will continue the forward momentum that has been building over the last 10 years. These new IAPAC initiatives are inspired by and consistent with the five objectives outlined above, and denote a new level of commitment on behalf of the association to the furtherance of Jonathan's vision of

a physician's role in the world, and in the sphere of HIV medicine.

It is important to note that none of the objectives noted above has a defined endpoint. Although IAPAC as an association has a clear direction in its forward movement, our goals are purposely open-ended, to allow for growth and changes in scope and focus. At the 10-year anniversary mark, IAPAC's direction has become clearer, more concentrated, and is greatly inspired by the idea that healthcare is a human right, and that physicians have the ability and the responsibility to make significant and lasting positive changes in the world. Our response has become even more pragmatic, imbued with a hard-won understanding that the basic priorities must not change, but that tactics and methods must be flexible in order to take advantage of opportunities as they present themselves. Indeed, never has our motto—"Battling Complacency. Advancing Commitment."—been more relevant.

This milestone would not have been possible without the support and hard work of our members. IAPAC members are heroes working in often-difficult conditions to defeat one of the deadliest diseases of the 20th century. We are honored to join you in a collective fight against HIV/AIDS. As we move forward, and look to our next 10 years, I am excited about the prospects for IAPAC and for our members, and I look forward to the many advances your support has made possible. ■

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



MESSAGE FROM THE CHAIRMAN

On the occasion of our 10th anniversary

Allen I. Freehling

Almost from its very inception, I have served on the Board of Trustees of the International Association of Physicians in AIDS Care (IAPAC), and during the last several years, my peers have asked me to serve as Chairman.

As a result of this remarkable, ongoing experience, I have had many an opportunity to gain insight regarding the scope of our activities; the staff who have allowed us to reach myriad goals; those corporate, foundation, and government sponsors which have provided us with the means to constantly go from strength to strength; the many thousands of caregivers, researchers, and educators whose tireless efforts are helping to mitigate the horrendous pandemic that we are attempting to surmount, and—most importantly—those men, women, and children who are struggling to survive the worldwide ravages which HIV/AIDS brings to their lives and to ours as we witness the many ways in which they refuse to let go of life itself until they are left with no other choice but to die.

On that latter note, though we have celebrated the fact that the pandemic is no longer necessarily a death sentence—thanks to the medical advances which are keeping alive those who are infected with the virus—none of us can rest on our laurels until, at long last, some ingenious scientist discovers a cure that will finally put an end to this tragic scourge... once and for all.

Since that time is not yet ours to have and to behold, we must accept the responsibility to remain vigilant in our efforts, which are designed to utilize the expertise of each person who chooses to provide medical



care to those who are afflicted with HIV/AIDS—wherever they live and regardless of the circumstances in which they find themselves.

Each member of IAPAC has, by definition, made a commitment to change the course of the pandemic. Both by working as physicians or other healthcare professionals with the people afflicted by this disease, and by donating time and money to IAPAC, you and the other members are already doing more than your share to bring some relief to those millions of people who are hardest hit. But all of you who are members of IAPAC are also aware that the world's efforts are falling short of what is needed to truly turn the tide.

This is why we should all stand in awe of IAPAC's staff—led and often driven by their and our extraordinary President/CEO, José M. Zuniga, whose vision, energy,

determination, and sense of purpose are wondrous indeed. Their and his determination to stay the course is most laudable indeed.

This is why we must be constantly grateful to those entities that generously fund our activities, programs, and projects in every corner of the world, where HIV/AIDS is being challenged by IAPAC and by those individuals and organizations with whom we are partners in this global enterprise.

This is why we need always pay tribute to the medical professionals—our members—who will not rest until a vaccine causes this pandemic to finally and at long last fade into history as another disease that we have overcome.

And, this is why our celebration of IAPAC's 10th anniversary, so we may remember everything that has occurred during the last decade, is appropriate; however, let us never forget that ours is the obligation to remind ourselves again and again of what we must do in the immediate and far-reaching future, to minimize the effects of the pandemic for each and every person who comes under its terrible influence, and then to renew our commitment to remain on point as long as we must.

Does IAPAC deserve to be congratulated? Of course!

Dare we say or think that we have done enough? Of course not... not as long as someone, some place is being infected; that someone, some place is attempting to do battle with this relentless foe!

Allen I. Freehling is Chairman of the IAPAC Board of Trustees, and he serves as Executive Director of the Los Angeles Human Relations Commission.

1995



TOP 10

10 Most Important Developments in HIV Medicine



1. Demonstration that the natural history of HIV infection is associated with production of an average 10^9 virions/day in patients with CD4 counts <500 cells/mm³.
2. Introduction of protease inhibitors (PIs) with US Food and Drug Administration (FDA) approval of saquinavir (SQV), and initial trials with indinavir (IDV) and zidovudine (ZDV).
3. Demonstration of the value of quantitative HIV RNA levels to determine prognosis.
4. Publication of US Public Health Service (PHS)/Infectious Disease Society of America (IDSA) Guidelines for prevention of opportunistic infections.



5. FDA approval of lamivudine (3TC) for combination antiretroviral therapy.
6. Demonstration that resistance to PIs is an ominous sign.
7. Demonstration of Kaposi's sarcoma viral etiology.
8. Publication of US AIDS Clinical Trials Group (ACTG) study 175 (and Delta Trial): Monotherapy with zidovudine (ZDV) became antiquated; the 1993 Expert Panel recommendations became decidedly passé; combination antiretroviral therapy was "in"; and didanosine (ddi) made a surprise showing.



9. Demonstration of the relative risk and role of ZDV in prevention of occupationally acquired HIV.
10. Publication of the epidemiology of AIDS in the United States: Reported cases exceed 500,000 as of October 1995, and the estimated prevalence in young adult men reaches 0.8 percent.

References

1. Ho DD, Neumann AU, Perelson AS *et al*. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature* 1995;373:123-126; Wei X, Ghosh SK, Taylor ME, *et al*. Viral dynamics in human immunodeficiency virus type 1 infection. *Nature* 1995;373:117-122.
2. Danner SA *et al*. A short-term study of the safety, pharmacokinetics, and efficacy of ritonavir, an inhibitor of HIV-1 protease. European-Australian Collaborative Ritonavir Study Group. *N Engl J Med* 1995;333:1528-1533.
3. Mellors J, Rinaldo CR Jr, Gupta P *et al*. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science* 1996;272:1167-1170; Mellors J, Kingsley LA, Rinaldo CR Jr *et al*. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. *Ann Intern Med* 1995;122:573-579.
4. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: a summary. *Ann Intern Med* 1996;124:349-368.
5. Eron JJ, Benoit SL, Jemsek J *et al*. Treatment with lamivudine, zidovudine, or both in HIV-positive patients with 200 to 500 CD4+ cells per cubic millimeter. North American HIV Working Party. *NEJM* 1995;333:1662-1669.
6. Condra JH, Schleif WA, Bhalaj OM *et al*. *In vivo* emergence of HIV-1 variants resistant to multiple protease inhibitors. *Nature* 1995;374:569-571.
7. Moore PS, Chang Y. Detection of herpesvirus-like DNA sequences in Kaposi's sarcoma in patients with and without HIV infection. *NEJM* 1995;332:1181-1185.
8. Publications were in 1996-1997: Hammer SM, Katzenstein DA, Hughes MD *et al*. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. AIDS Clinical Trials Group Study 175 Study Team. *New Engl J Med* 1996;335:1081-1090; Delta: a randomized double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. Delta Coordinating Committee. *Lancet* 1996;348:283-291.
9. Case-control study of HIV seroconversion in health-care workers after percutaneous exposure to HIV-infected blood—France, United Kingdom, and United States, January 1988-August 1994. *MMWR Morb Mortal Wkly Rep* 1995;44:929-933.
10. US Centers for Disease Control and Prevention. First 500,000 AIDS cases—United States, 1995. *MMWR* 1995;44:849-853; Rosenberg PS. Scope of the AIDS epidemic in the United States. *Science* 1995;270:1372-1375.



PIs associated with increased risk of cardiovascular disease

Michael Carter

HIV-positive patients who take a protease inhibitor (PI) as part of their antiretroviral regimen have a significantly increased risk of cardiovascular events, according to research published last month in the journal *HIV Medicine*.¹

There has been a dramatic fall in the incidence of HIV-related illness and death in HIV-positive individuals since highly active antiretroviral therapy (HAART) became available. However, cardiovascular illness has been seen with increasing frequency in HIV-positive patients since effective antiretroviral drugs became available. It has been suggested that antiretroviral drugs, particularly PIs, are at least partly responsible for the increasing amount of cardiovascular illness seen in HIV-positive patients. However, other possible causes have also been suggested. It has also been noted that HIV-positive individuals appear to have a higher prevalence of traditional cardiovascular risk factors, such as smoking. In addition, thanks to the success of antiretroviral therapy, many people taking HAART are now living to an age when they might become vulnerable to cardiovascular disease.

A team of researchers from Bristol-Myers Squibb, the US Centers for Disease Control and Prevention (CDC), and Johns Hopkins University obtained data from a large longitudinal database to answer the question: "Does PI exposure increase the risk of cardiovascular disease in HIV-infected patients after adjusting for known cardiovascular disease risk factors?"

Editor's Note: This article was first e-published February 9, 2005, at www.aidsmap.com.

HIV Insight™, a prospective observational database, provided the study population. Patients aged over 18 years who attended at least two medical consultations between 1996 and 2003 were eligible for inclusion in the investigators' analysis. Demographic and cardiovascular risk data were extracted and information was obtained on the date when a PI-containing antiretroviral regimen was first initiated, or (for non-PI-treated patients), the date when antiretroviral therapy was first initiated.

For the purpose of the study, cardiovascular events included acute myocardial infarction, angina pectoris, coronary artery disease, angioplasty, coronary bypass, cerebrovascular accident, and peripheral vascular disease.

Risk factors for cardiovascular disease included high blood lipids, use of lipid lowering therapy, high blood pressure, diabetes, and smoking. Data were also obtained on injecting drug use, cocaine use, and weight. Family history of cardiovascular disease was not included in the investigators' analysis, as this information was not recorded in the database.

A total of 7,542 patients were included. The median duration of follow-up was significantly longer for patients who were treated with a PI (3.5 years versus 2 years, $p < 0.001$). Individuals who took a PI were significantly older ($p < 0.001$), were more likely to be male (88 percent versus 80 percent, $p < 0.001$), to be of white race (61 percent versus 50 percent, $p < 0.001$), and had higher rates of pre-existing hypertension (10 percent versus 5 percent, $p < 0.001$). However, patients who took a PI were less likely to smoke (34 percent versus 39 percent, $p < 0.002$).

In total, 127 events of cardiovascular disease occurred. The overwhelming majority of these (112) occurred among

patients taking a PI. The adjusted incidence of cardiovascular disease was 9.8 per 1,000 patient years for patients taking a PI compared to 6.5 per 1,000 patient years for HIV-positive patients not prescribed a PI ($p = 0.008$). When the investigators restricted their analysis to the subset of patients aged 35 to 65 years, they still found that cardiovascular events were significantly more likely to occur in patients taking a PI than in patients who were not (11.5 per 1,000 patient years versus 8 per 1,000 patient years, $p = 0.01$).

In multivariate analysis, the investigators established that more than 60 days cumulative therapy with a PI was associated with a statistically significant increase in the risk of cardiovascular disease ($p = 0.03$).

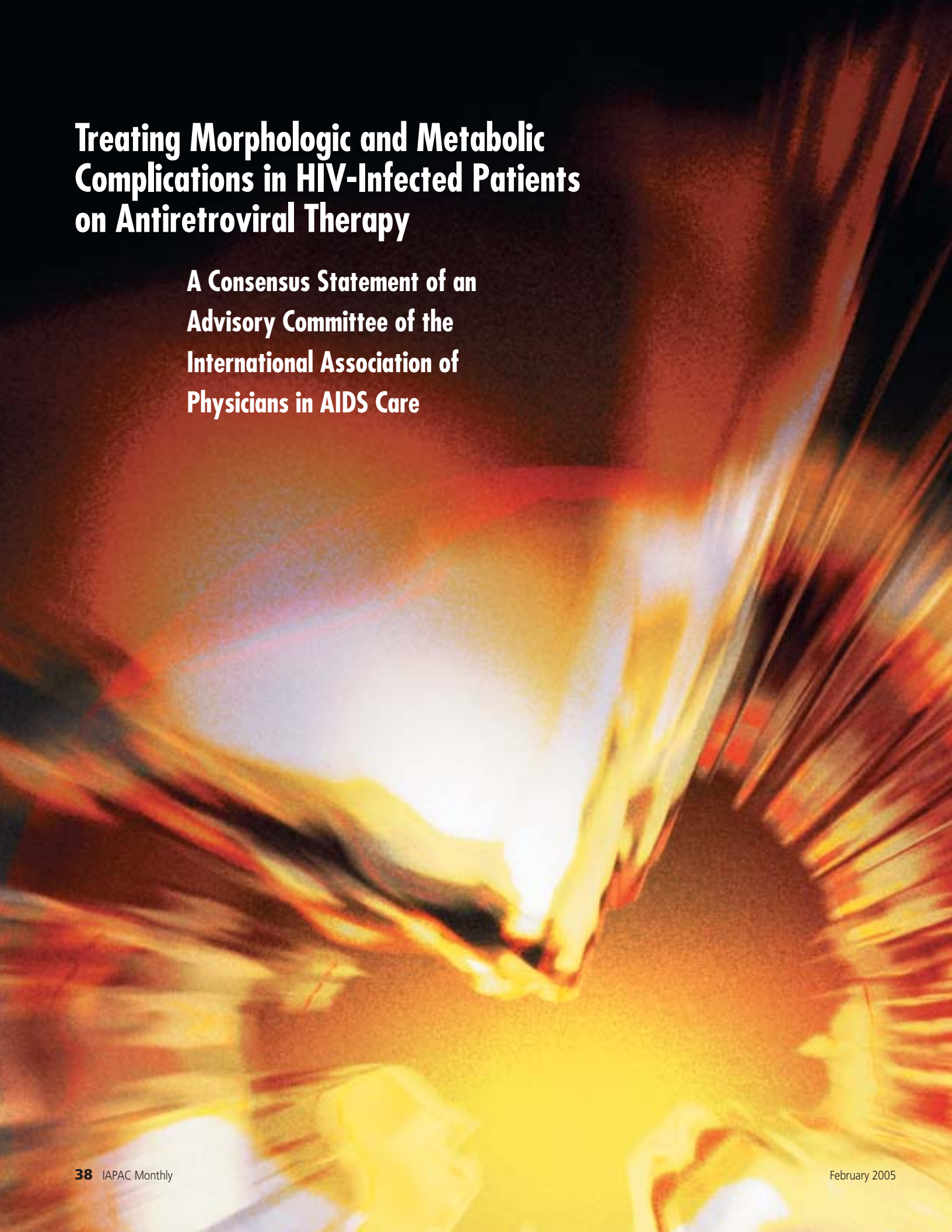
However, they also found that many of the traditional risk factors for cardiovascular disease were significant as well, including current smoking ($p < 0.001$), past smoking ($p = 0.03$), age over 65 years ($p < 0.001$), diabetes ($p = 0.006$), and pre-existing cardiovascular disease ($p < 0.001$).

In further sensitivity analyses, over a year of treatment with a PI was shown to increase the risk of cardiovascular disease for patients in the 35-65 age group (adjusted hazard ratio, 1.6).

According to the investigators, "the results of this analysis suggest an increased cardiovascular disease event rate in HIV-infected patients exposed to [PI] therapies." They conclude that physicians should evaluate the cardiovascular disease risk of patients currently taking, or about to initiate, HAART. ■

Reference

1. Iloeje U, Yuan Y, L'italien G, et al. Protease inhibitor exposure and the increased risk of cardiovascular disease in HIV-infected patients. *HIV Med* 2005;6:37-44.

The background of the page is an abstract, artistic composition. It features a central, bright, glowing point from which numerous thin, radiating lines of light extend outwards, creating a starburst or lens flare effect. The color palette is dominated by warm tones, including deep reds, oranges, yellows, and browns, with some cooler blue and purple hues interspersed. The overall texture is grainy and painterly, suggesting a digital or photographic origin. The light streaks are most prominent on the right side, where they appear to converge towards the center.

Treating Morphologic and Metabolic Complications in HIV-Infected Patients on Antiretroviral Therapy

**A Consensus Statement of an
Advisory Committee of the
International Association of
Physicians in AIDS Care**

¹University of Cincinnati; ²Harvard Medical School; ³Columbia University College of Physicians and Surgeons; ⁴AIDS Research and Treatment Center of the Treasure Coast, Ft. Pierce, FL; ⁵Brigham and Women's Hospital, Boston; ⁶Mercy Hospital, Miami; ⁷University of Pennsylvania School of Medicine, Philadelphia

Objective: Clinicians are increasingly challenged by presentation of morphologic and metabolic complications in HIV-infected patients. These complications are associated with HIV infection and/or combination antiretroviral therapy. This Consensus Statement is intended to offer guidance to clinicians actively involved in HIV/AIDS care.

Participants: Seven clinicians with expertise in HIV medicine were invited by the International Association of Physicians in AIDS Care (IAPAC) to serve on an ad hoc Advisory Committee.

Consensus process: IAPAC convened the Advisory Committee to develop a draft Consensus Statement. Each clinician was tasked with drafting a specific section of the Consensus Statement corresponding with his or her expertise around a morphologic and/or metabolic complication. Scientific and clinical research, and other data in published literature and abstracts from scientific conferences were considered by strength of evidence. This document represents the consensus agreement of the Advisory Committee.

Conflict of interest disclosure: IAPAC sponsored and coordinated the development of this Consensus Statement with an unrestricted educational grant from Bristol-Myers Squibb. The opinions expressed in this Consensus Statement represent only those of the Advisory Committee.

Background

Treatment of HIV-infected patients is frequently complicated by several morphologic and metabolic complications. These complications include:

- Lipoatrophy
- Fat accumulation
- Insulin resistance and diabetes
- Dyslipidemias and cardiovascular disease
- Bone disease
- Lactic acidemia/acidosis

Unfortunately, the mechanisms underlying these complications largely remain unknown. And, although various guidelines exist for treating HIV-infected patients with such complications, the recommendations offered are often not particularly

Editor's Note: As a service to members of the International Association of Physicians in AIDS Care (IAPAC), this issue of the IAPAC Monthly features a preview of "Treating Morphologic and Metabolic Complications in HIV-Infected Patients on Antiretroviral Therapy: A Consensus Statement of an Advisory Committee of the International Association of Physicians in AIDS Care," which will be published in the April/June 2005 issue of IAPAC's clinical journal, *JIAPAC*.

user-friendly for the typical HIV care provider. In addition, these guidelines do not account for the compound effects of HIV infection or the effects that may be caused by altering and/or combining antiretroviral therapy (ART) with other therapeutic drugs. Consequently, an Advisory Committee of the International Association of Physicians in AIDS Care (IAPAC) was convened to propose practical recommendations for managing HIV-infected patients on ART who present with morphologic and metabolic complications, with the ultimate goal of optimizing treatment outcomes and improving patient quality of life.

Lipoatrophy

Lipoatrophy is the most common morphologic abnormality associated with HIV and its therapy, and the highly distressing and potentially stigmatizing effects from this complication on patients' quality of life should not be underestimated.¹ The typical presentation consists of facial, limb, and buttock wasting; prominence of the veins on the arms and legs; and greater definition of the individual muscles. Unlike HIV-related wasting seen before the availability of potent ART, lean body mass in patients with lipoatrophy often shows little or change.²

Incidence and risk factors. In a prospective cohort study comparing men with and without HIV, self-reported facial lipoatrophy of at least mild severity occurred in 42 percent of those with HIV on protease inhibitor (PI)-containing ART versus only 3 percent of seronegative controls. In contrast, fat accumulation occurred with equal frequency in both groups over time.³ The preliminary findings in the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) cohort study⁴ strongly indicate that fat atrophy is the dominant component of the so-called "lipodystrophy syndrome," and that there is no relationship between fat atrophy and fat accumulation; hence, there is no redistribution of fat from subcutaneous stores to the abdominal visceral area as had previously been hypothesized.

Both patient- and treatment-related risk factors for lipoatrophy have been identified. The most important patient-related risk factor for lipoatrophy is the stage of HIV disease: patients who have a lower CD4 count at the time of starting treatment are at substantially greater risk.⁵ Other identified associations include duration of HIV infection and age, but lipoatrophy may still occur in a subset of patients in the absence of long-standing HIV infection or advanced HIV-related immunosuppression,

even including those treated for acute HIV infection.

The best data regarding treatment-associated risk comes from prospective comparative clinical trials. A proposed hierarchy of treatment-associated risk for lipotrophy is as follows: dideoxynucleosides—stavudine (d4T), didanosine (ddI), and zalcitabine (ddC)—carry the highest risk; zidovudine (ZDV) is intermediate; and tenofovir (TDF), abacavir (ABC), and lamivudine (3TC) should be associated with the lowest risk.⁶⁻⁸ The consistent observations that d4T-containing regimens are associated with a higher risk of developing lipotrophy have led to a change in some treatment guidelines in which d4T is no longer recommended as a component of preferred first-line antiretroviral (ARV) regimens.⁹ This change was likely related not only to lipotrophy, but also to other manifestations of mitochondrial toxicity. Although PIs have been more directly linked to insulin resistance and fat accumulation, the combination of nucleoside reverse transcriptase inhibitors (NRTIs) and PIs appears to act synergistically to accelerate fat loss.¹⁰ Other contributing factors are likely as well.¹¹

Pathogenesis. The precise mechanism by which HIV therapy induces fat atrophy is still under investigation. The current leading hypothesis is that NRTI-induced mitochondrial toxicity induces fat cell apoptosis, with the risk greatest for those agents demonstrating the highest *in vitro* inhibition of the mitochondrial enzyme polymerase gamma. In addition, it has been demonstrated that HIV itself may lead to reduced cellular mDNA content compared with HIV-negative controls,^{12, 13} rendering those with HIV more susceptible to the toxic effects of treatment. However, other studies suggest there is no relationship between mitochondrial toxicity and the development of lipotrophy.^{12,14}

Management. Because the underlying pathogenetic mechanism(s) remain unclear, management strategies have met with limited success. Strategies consist of drug substitutions, insulin-sensitizing agents, and cosmetic surgery. Because these treatments are either relatively ineffective or costly, strategies to prevent the occurrence of lipotrophy, such as selection of ARV regimens with low mitochondrial toxicity, are critically important.

Several clinical studies have shown that substitution of ABC for d4T leads to a gradual increase in limb fat that is often accompanied by a subjective improvement in facial appearance.¹⁵⁻¹⁷ Levels of mDNA content also improve in adipose cells, although peripheral blood mononuclear cells may or may not show improvement. It is not known if TDF would have the same effect, although this is presently under study. Substituting a nonnucleoside reverse transcriptase inhibitor (NNRTI) for the PI component of the regimen has had no consistent effect on morphologic changes.¹⁸

Three prospective clinical trials have evaluated rosiglitazone in HIV-related lipotrophy; two showed no effect,^{19,20} and one demonstrated a modest but statistically significant improvement.²¹ Metformin is another insulin-sensitizing agent that has been studied in patients with HIV-related body habitus changes; however, treatment is associated with weight loss²² and hence should be avoided in cases of marked lipotrophy.

Unlike the various pharmacologic interventions for lipotrophy, which induce relatively small benefits, cosmetic surgery is often extremely successful and can dramatically improve appearance. Reported techniques include autologous fat transfer²³ or, more commonly, injection of biologically inert substances such as polylactic acid.^{24,25} Patient satisfaction after polylactic acid injection is extremely high, and thus far the procedure appears safe. The major drawbacks to this treatment approach are the lack of long-term efficacy and safety data, the relatively high cost, and the lack of effect on lipotrophy of the arms and legs. Patients referred for this procedure should be informed that most insurance policies and no state-funded programs cover the cost of this treatment.

Fat accumulation

Accumulation of fat in the abdomen, dorsocervical area, and other depots was an early observation in patients on combination ART preceding the use of PIs.^{26,27}

Incidence and risk factors. Determining the incidence and prevalence of fat accumulation is difficult in the absence of specific diagnostic criteria, which do not exist. Based upon self-report with observer confirmation, about one third of treated, HIV-infected patients will show evidence of intra-abdominal (visceral) fat accumu-

lation in the presence or absence of more generalized obesity.²⁸ Between 5 percent and 10 percent of patients will demonstrate more generalized upper body obesity, including a prominent dorsocervical fat pad. Similar findings have been observed in both men and women, and both visceral and dorsocervical fat accumulation has been reported in children.²⁹ There is some evidence in favor of racial and gender influences on prevalence. The interrelationships among fat accumulation and other manifestations of HIV-associated lipodystrophy are uncertain.

Pathogenesis. The pathogenetic mechanisms underlying the accumulation of fat in visceral or other fat depots are uncertain. Early observations showed evidence of fat accumulation in the presence of NRTI-containing therapy, although no potential mechanisms have been theorized to explain how NRTIs might promote fat accumulation. Some element of immune reconstitution, as opposed to ART, might be involved, but no study or hypothesis has specifically targeted a relationship to fat accumulation.

It is possible that visceral fat accumulation represents, in part, the development of the metabolic syndrome in those who are genetically predisposed. Various studies have estimated that between 15 percent and 25 percent of the population contains a genetic predisposition to developing the cluster of metabolic alterations referred to as the metabolic syndrome, and it is likely that a similar proportion of HIV-infected patients have these same genetic predispositions.

Screening/diagnosis. Aside from changes that would be obvious to any observer, there are neither accepted diagnostic criteria for visceral fat accumulation, nor are there generally accepted published normal values and measurements of these values. Hence, clinical estimation of visceral fat will be possible only by anthropometric means for the indefinite future, much as is the case for diagnosing the metabolic syndrome. It is likely that criteria adopted for diagnosis of the metabolic syndrome (eg, waist size >102 cm in men) would be excessively conservative, because many HIV-infected patients have abdominal subcutaneous lipotrophy such that a higher proportion of abdominal fat is visceral in HIV-infected patients. In one study, a composite criterion of waist circumference >88 cm and a waist/hip ratio >0.95 in men, plus waist circumference

>75 cm and a waist/hip ratio >0.90 in women effectively detected patients with high visceral fat content, but also may have been excessively conservative.³⁰ These criteria have not been subjected to independent validation, and further validation is required.

Management. There are no known ways to avoid the development of visceral fat accumulation except perhaps with the prevention of weight gain. Switching ARV drugs has not been shown to be effective in reducing visceral fat content in the absence of disease progression. In patients with increased fat sufficient to produce symptoms, diet and weight loss may be tried. A weight loss of 8 percent to 10 percent may be associated with symptomatic relief and some reduction in fat, although excessive weight loss increases the risk of visible lipodystrophy. Pilot studies showed that resistance exercise may decrease trunk fat.³¹ Weight loss and decreased waist size were noted in a trial of metformin, which was used to increase insulin resistance.²² Recombinant growth hormone has been shown to decrease visceral fat content in several clinical studies, and the optimal dose and duration of therapy are currently being determined.^{32,33} Cosmetic surgery may be an option for the management of large dorsocervical fat pads, although the risk of recurrence exists. The US Food and Drug Administration (FDA) has approved no pharmacologic therapy for this complication.

Insulin resistance and diabetes

Type 2 diabetes mellitus and insulin resistance, considered a precursor state to diabetes, are increased among HIV-infected patients.

Incidence and risk factors. Recent reports have identified an increased risk of impaired glucose tolerance, hyperinsulinemia, and Type 2 diabetes among HIV-infected patients compared to the general population.³⁴⁻³⁷ In most of the studies evaluating insulin resistance and diabetes in this population, traditional risk factors such as increased age, obesity, and being African-American or Hispanic remained significant. Furthermore, several studies have identified PI use and/or combination ART in general as conferring additional risk for diabetes development. Hepatitis C virus (HCV) infection is a known risk factor for Type 2 diabetes in the general population³⁸ and has now been shown to increase

the risk of diabetes among HIV/HCV-coinfected patients.³⁹ Diabetes and impaired glucose tolerance are known independent risk factors associated with cardiovascular disease, and may be important factors in the long-term health of HIV-infected patients. In a large prospective study of more than 23,000 HIV-infected patients, a diagnosis of diabetes was associated with an increased rate of myocardial infarction.⁴⁰

Pathogenesis. Several mechanisms may be responsible for the increased rates of insulin resistance and diabetes observed among HIV-infected patients. For example, PIs have been shown to induce insulin resistance in healthy, non-HIV-infected individuals and are implicated in dysregulation of glucose homeostasis in HIV-infected patients on ART.⁴¹ In addition, changes in body fat distribution, both increased central adiposity and peripheral fat atrophy, may contribute to insulin resistance in patients with HIV lipodystrophy.^{42,43}

Screening/diagnosis. Given the increased risk of Type 2 diabetes identified in association with HIV infection and the use of ART, an annual fasting plasma glucose (FPG) test is recommended and should be performed in conjunction with annual fasting lipid profiles. A diagnosis of diabetes can be made by FPG >126 mg/dl or a glucose concentration >200 mg/dl following a two-hour oral glucose challenge. In both cases, a positive result should be confirmed with a repeat test on another day. There is no established clinical test for the diagnosis of insulin resistance; however, impaired fasting glucose (IFG) (fasting glucose >110 mg/dl and <126 mg/dl) and impaired glucose tolerance (IGT) (a two-hour glucose \geq 140 and <200 mg/dl) are considered indicative of a pre-diabetic state. If IFG or IGT are present, or if additional risk factors such as HCV coinfection, obesity, and PI use are present, annual oral glucose tolerance testing is suggested. Fasting insulin levels may also be measured; however, there is considerable variability in insulin assays and no established norms among endocrinologists for clinical purposes.

Management. The clinical management of Type 2 diabetes is the same as in the general population. Management should begin with recommendations and counseling on dietary and lifestyle modifications. Insulin-sensitizing agents should also be considered in the management

of Type 2 diabetes in HIV-infected patients. A number of studies conducted in the context of lipodystrophy have demonstrated preliminary safety and efficacy in improving insulin sensitivity.^{19,20,22,34,44,45} Use of metformin can result in weight loss and therefore may be preferred for patients with relative central adiposity or obesity, whereas thiazolidinediones may provide improvement in fat atrophy.^{22,34,45} However, rosiglitazone has been associated with increases in low-density lipoprotein (LDL) cholesterol in both non-HIV-infected and HIV-infected patients and therefore should be used with caution in this population already at risk for hyperlipidemia.⁴⁶

Lipid abnormalities and cardiovascular disease

Although the benefits of ART are undisputed, there is growing concern regarding the association of increased cardiovascular risk and the dyslipidemias associated with HIV infection and ART.

Incidence and risk factors. Most studies clearly suggest that there is an increase in coronary artery disease (CAD) in HIV-infected patients compared with age-matched controls.⁴⁷⁻⁵³ Multiple observational cohort studies have been performed to determine if lipid elevations and metabolic perturbations induced by ART increase the rate of cardiovascular events. These studies, although not uniformly positive,⁵⁴ have linked ART to a greater risk of myocardial infarction. Other studies have shown that ART is associated with a greater risk of dyslipidemia. However, some of the lipid increases after initiation of ART appear to be a return to baseline levels that were previously depressed due to HIV infection.⁵⁵ It is clear that lipid levels in patients on ART frequently go beyond baseline levels, and high-density lipoprotein (HDL) levels remain lower than expected. In addition, short-term trials in uninfected subjects have demonstrated potent lipid-raising effects of several ARV drugs.⁵⁶

Although dyslipidemia was originally attributed primarily to PIs, more recent studies have shown that specific NRTIs can also affect lipid levels. In particular, d4T has been found to produce greater elevations in cholesterol and triglyceride (TG) levels than TDF,⁵⁷ and switching from d4T to TDF leads to improvements

in lipid levels.⁵⁸ In a large randomized trial in ART-naïve patients, ABC was more likely to increase cholesterol and TG levels than ZDV.⁵⁹ NNRTIs have also been associated with different lipid effects and generally result in elevations of total cholesterol without much effect on TG levels. In the 2NN study, nevirapine (NVP) was compared to efavirenz (EFV) and was found to be associated with larger increases in HDL cholesterol and larger decreases in the more favorable total cholesterol:HDL cholesterol ratio.⁶⁰

Studies investigating the effects of HIV infection and/or ART on measures of vascular endothelial structure and function have been reported. For example, several studies have been conducted in HIV-infected patients and have shown greater carotid artery intima-media thickness (CIMT) in patients on ART compared with controls.^{61,62} One longitudinal study showed a more rapid progression in CIMT after one year in HIV-infected patients on predominantly PI-based ART compared to HIV-negative matched control patients.⁶² Cardiac computed tomography with coronary artery calcium (CAC) scoring has shown some negative results when HIV-infected patient cohorts have been studied;⁶³ however, other studies have shown that patients on PIs had significantly higher CAC scores compared with untreated patients or patients on NNRTI-based regimens.^{64,65} In the aggregate, these surrogate marker studies are consistent with the large cohort outcome trials, and they validate the concern regarding potential premature development of atherosclerosis in HIV-infected patients on ART.

Screening/diagnosis. Lipid screening should be performed by means of an annual fasting lipid profile. Routine use of National Cholesterol Education Program (NCEP) guidelines should be considered to categorize patients into low, intermediate, and high risk of cardiovascular complications. (Table 1) For patients at high risk for CAD, exercise stress testing, preferably Thallium-type testing, should be considered in a similar manner as for non-HIV-infected, high-risk patients.

CIMT measurement is a sensitive indicator of atherosclerosis and adds predictive value to standard risk factor assessment tools.^{66,67} CIMT has also been used to track the progression or regression of atherosclerosis in response to therapeutic

Table 1. LDL-c goals for drug therapy according to risk category

Risk category	LDL-c goal (mg/dL)*	LDL-c level indicative of drug therapy (mg/dL)
CHD or CHD risk equivalent (10-year risk >20%)	<100	≥130
≥2 risk factors (10-year risk ≤20%)	<130	10-year risk: <10%: ≥160 10%-20%: ≥130
≤1 risk factor	<160	≥190

LDL-c: low-density lipoprotein cholesterol; CHD: coronary heart disease

*Initiate therapeutic lifestyle changes if at or above this level; LDL-lowering drug optional if below this level.

For use of non-HDL-c, add 30 mg/dL to each target level for treatment indication or goal of therapy.

interventions.⁶⁸ Performing CIMT is not feasible, however, for most providers; while CAC is more widely available. CAC determination is a sensitive indicator of the presence of coronary artery atherosclerosis,⁶⁹ but whether it should be adopted as a screening test remains controversial. Patients referred for this procedure should be informed that most insurance policies and no state-funded programs cover the cost of this treatment.

Management. The management of HIV-infected patients with dyslipidemia and/or coronary heart disease (CHD) should include monitoring and optimizing lipid levels through lifestyle changes, switching ARV drugs, and the utilization of specific lipid-lowering treatments. In HIV-infected patients, the use of lipid-lowering drugs may result in pharmacokinetic interactions with ARV drugs, thereby complicating clinical management of these patients. In the absence of randomized clinical trials, clinicians should aggressively treat atherogenic dyslipidemia by utilizing or switching to ARV drugs with the lowest potential to induce CHD. When such a treatment strategy is not possible or proves ineffective, clinicians should prescribe lipid-lowering therapy.

For HIV-infected patients at risk for cardiovascular disease, comprehensive reviews of guidelines have been published by several organizations,⁷⁰⁻⁷² which align closely with recommendations for managing non-HIV-infected subjects at risk.⁷³ The emphasis is on treatment of elevated low-density lipoprotein (LDL)-c modified by specific risk factors including cigarette smoking, blood pressure, HDL-c levels, family history of CHD, and older age.⁷³ Treatment should start with therapeutic lifestyle changes including diet, increasing soluble fiber, reducing the intake of saturated fats and cholesterol, reducing weight, and

increasing physical activity.

In patients for whom lifestyle changes fail, clinicians should first consider switching ART. Switching to a triple-NRTI-, NNRTI-, or atazanavir (ATV)-based ARV regimen (the latter being our preferred choice) has been shown to improve lipid profiles in patients who have developed dyslipidemia while on PI-based regimens.^{74,75} The likelihood of virologic failure has ranged from 10 percent to 15 percent in most published trials of ART switch studies.⁷⁴ Unfortunately, at the present time there are no studies comparing the strategy of switching ART for dyslipidemia versus treatment with lipid-lowering agents. If deemed virologically safe, it is preferable to switch therapy, thereby avoiding increasing the burden of pills ingested daily, the increased costs of additional therapy, and the potential for adverse drug-drug interactions. Those patients who do require a PI-based regimen may consider switching to ATV (unboosted by ritonavir [RTV] in treatment-naïve patients prior to current therapy, or RTV-boosted for the treatment-experienced) because of its lesser effects on lipid or glucose metabolism. Switching from a PI-based regimen to a triple-NRTI regimen is limited by higher rates of virologic failure, especially in those with prior non-suppressive ART or documented NRTI resistance.

Lipid-lowering therapy is recommended when the above measures fail to reach the desired targets. Treatment should be directed to the specific lipid disorder. (Table 2) The HMG CoA reductase inhibitors, or statins, are generally the first-choice therapy for elevated LDL-cholesterol.⁷⁶ Statins typically result in a 30 percent to 50 percent reduction in LDL-cholesterol and a 20 percent to 30 percent reduction in TG levels. Due to recognized interactions of some of

Table 2. Lipid-lowering therapy in HIV-infected patients

	TC	TG	HDL	LDL
Pravastatin ⁸⁷ (n = 15)	-1.23 mmol/L	-0.31 mmol/L	0.06 mmol/L	-1.2 mmol/L
Pravastatin ⁸⁴ (n = 86)	-41 mg/dL	-27 mg/dL	No Δ	-30 mg/dL
Atorvastatin ⁸⁸ (n = 10)	-19%	-21%		
Gemfibrozil ⁸⁸ (n = 25)	-32%	-57%		
Gemfibrozil ⁸⁹ (n = 8)	No Δ	-83%		
Fibrates ⁹⁰ (n = 66)	-22%	-41%		
Statins ⁹⁰ (n = 37)	-25%	-35%		
Prav+Feno ⁸⁴ (n = 130)	-16%	-38%	16%	-10%
Ator+Gem ⁸⁸ (n = 19)	-30%	-60%		
Fenofibrate ⁹¹ (n = 13)	-6.6%	-45.7%		
Fenofibrate ⁸⁴ (n = 88)	-15 mg/dL	-118 mg/dL	4 mg/dL	13 mg/dL

TC: total cholesterol; TG: triglycerides; HDL: high-density lipoprotein; LDL: low-density lipoprotein

these agents with PIs, most authorities recommend initiation of pravastatin (20 mg daily) or atorvastatin at low doses (10 mg daily) with careful monitoring for adverse events.^{70,77} If no adverse events have occurred or lipid levels have not improved after six to eight weeks, the dose may be increased.^{71,78} Based upon numerous pharmacokinetic studies, simvastatin and lovastatin should not be used in HIV-infected patients taking PIs.^{72,79} The newer statin, rosuvastatin, is not primarily metabolized by CYP450 enzymes similar to pravastatin, but there are currently no data assessing its potential interactions with ARV drugs.⁸⁰ Pravastatin levels decrease significantly (~50 percent) in the presence of most PIs, and doses may need to be increased to improve efficacy. A recent pharmacokinetic study demonstrated that simvastatin, atorvastatin, and pravastatin levels are decreased in the presence of EFV, suggesting that the lipid-lowering benefits of statins will be diminished in the presence of NNRTIs (EFV and NVP) that induce the metabolism of CYP3A4.⁸¹ Ezetimibe may result in a 10 percent to 20 percent reduction in LDL-c and has been shown to be synergistic when used with a statin.⁸²

Fibrates (eg, gemfibrozil) or fenofibrates are useful for the treatment of elevated TG levels. (Table 2) Treatment of hypertriglyceridemia should be based upon measurement of non-HDL-cholesterol levels (TC-HDL-c) that simultaneously take into account both atherogenic and cardioprotective lipid fractions. Fibrates generally induce reductions in TG by ~50 percent and increases in HDL-c by 5

percent to 10 percent (patients with very high TG levels may observe a rise in LDL-c when initiating fibrates). Fibrates are less likely to interact with PIs since they are not metabolized by the CYP450 system. Theoretically, they can be combined with statins to produce an additional TG-lowering effect. It appears that they may be appropriate in patients with hypertriglyceridemia and can reduce TG levels to normal (success observed in 64 percent of patients on PIs).^{70,74,83} Fenofibrate has been shown to lower TG by more than 50 percent and, when used in sequential combination with pravastatin, can help HIV-infected patients with combined hyperlipidemia reach NCEP Adult Treatment Panel (ATP) III goals.⁸⁴

Niacin has not been shown to be safe in treating HIV-infected patients; pending the results of ongoing clinical studies in this population, it should not be used except in highly refractory cases. Studies show it does work, but at the expense of worsening insulin resistance.⁸⁵ Fish oil (omega-3 fatty acids) may be effective in providing a 15 percent to 20 percent reduction in TG levels.⁸⁶ An algorithm is provided to facilitate the management of dyslipidemia in HIV infection. (Figure 1)

Bone disease

Osteopenia/osteoporosis is a frequent problem among HIV-infected patients. Osteopenia carries a two-fold lifelong increased risk of fracture, whereas osteoporosis increases the risk four-fold.⁹² Other bone complications, such as avascular necrosis (AVN) of the hip, have also been reported.⁹³

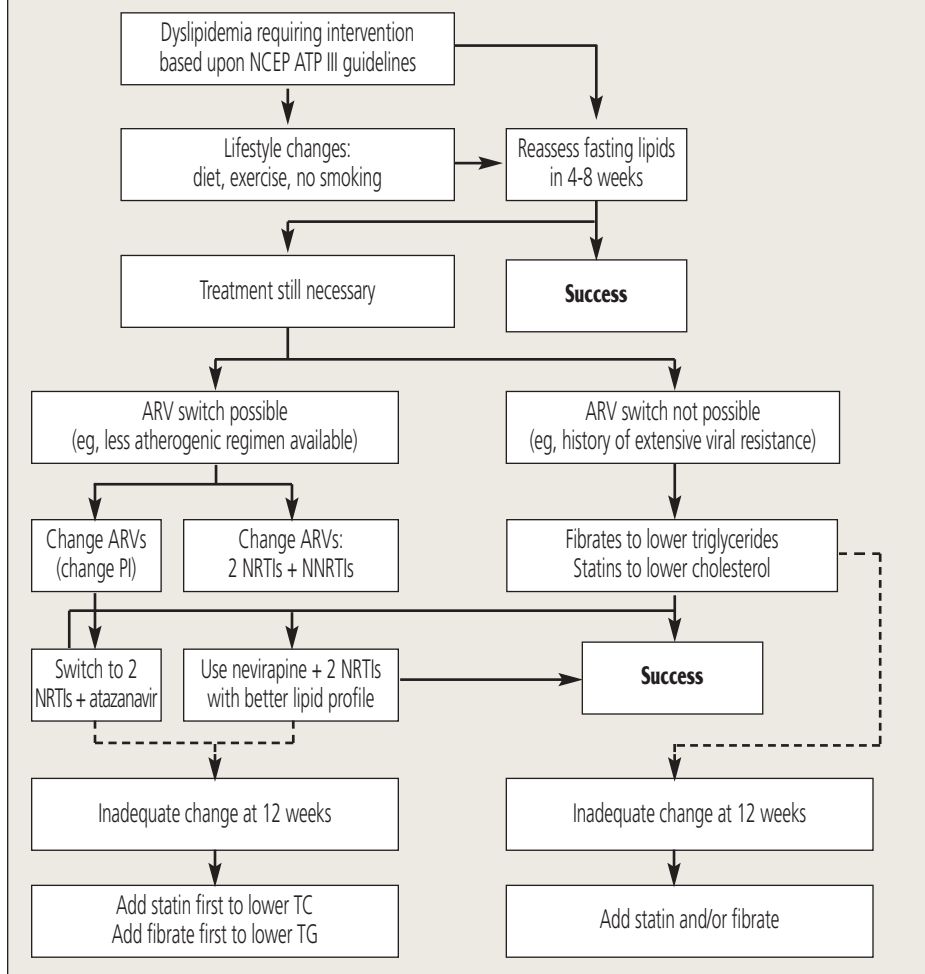
Incidence and risk factors. The frequency of osteopenia/osteoporosis varies between 28 percent in ART-naive patients⁹⁴ to 40 percent to 50 percent in patients with more advanced HIV disease,⁹⁵⁻⁹⁷ making this one of the most frequent metabolic complications associated with HIV disease. HIV-infected patients frequently have other risk factors that predispose them to develop osteopenia.⁹⁷ PIs were initially implicated in what was then considered to be a new side effect of therapy, but it is now clear that osteopenia and osteoporosis can occur in the absence of ART.⁹⁸

Pathogenesis. The relative contribution of ART and HIV infection itself to the development of this complication, and its relationship with other metabolic complications such as lactic acidosis, lipodystrophy, and hyperlipidemia is still under study.⁹⁹ The osteopenia/osteoporosis seen in HIV-infected patients on ART is associated with a state of high bone turnover with increased levels of bone formation and resorption.¹⁰⁰

Screening/diagnosis. Because of the high frequency of osteopenia and osteoporosis in HIV-infected patients, serious consideration should be given to evaluating the bone mineral density (BMD) of all such individuals, especially if other risk factors are also present. BMD of the spine and hip is normally measured using dual energy x-ray absorptiometry (DEXA scans). The World Health Organization (WHO) defines osteopenia and osteoporosis by comparison to normalized measurements of BMD. The t-score is the number of standard deviations (SDs) that a specific measurement differs from the normal BMD of the population at 30 years of age. Osteoporosis is defined as having a t-score <-2.5 SDs. Osteopenia is defined as a t-score between -1 and -2.5 SDs.

Management. For patients with established osteoporosis, a small study (100) has demonstrated the effectiveness of alendronate in combination with vitamin D and calcium, with increases in lumbar BMD equivalent to the ones seen in HIV-negative individuals (approximately 5 percent at 48 weeks). For patients with osteopenia, management should focus on lifestyle changes including discontinuation of tobacco use, increasing weight-bearing exercise, and an adequate intake of calcium and vitamin D together with ART. Other alternatives that have been used in the general population are not particularly

Figure 1. **Algorithm for managing dyslipidemia in HIV-infected patients**



useful in HIV-infected patients: estrogens can only be used in postmenopausal women, thiazides are only modestly effective and seem to work less well in males, parathyroid hormone might not be indicated in cases of high bone turnover, and calcitonin is very expensive and less effective than bisphosphonates. Switching ART does not seem to have a significant impact on BMD.¹⁰¹

Lactic acidemia/acidosis

Asymptomatic elevation of blood lactate (hyperlactatemia), generally defined as a venous lactate concentration >2-5 mmol/L with a normal arterial pH, is common in HIV-infected patients on NRTI-containing ART. Lactic acidosis (LA), defined as a venous lactate concentration >2 mmol/L plus arterial pH <7.30 (or [HCO₃]⁻ <20 mmol/L), although rare, is a very serious complication of ART. Moreover, LA with a venous lactate concentration >5 mmol/L is almost invariably symptomatic.

Incidence and risk factors. In general, asymptomatic hyperlactatemia has been found to occur in 8 percent to 21 percent of patients on NRTI-containing ART compared with 1 percent to 2 percent of untreated patients.¹⁰²⁻¹⁰⁴ Variability in assessing the incidence exists due to the technical difficulties in accurately measuring lactate levels and the lack of consistency in defining hyperlactatemia. However, when strict definitions/guidelines are used with uniform sampling techniques, the true prevalence has most recently been reported to be <3.5 percent.¹⁰⁵ Symptomatic hyperlactatemia has been reported to occur in ~1.5 percent to 2.5 percent of patients with an incidence of four to 10 cases per 1,000 patient years of treatment, whereas LA is even rarer with an estimated incidence of 1.3 cases per 1,000 patient years.^{102,103,106}

A small percentage of patients on NRTI-containing ART develop mitochondrial toxicity and hyperlactatemia or LA.

Severe hyperlactatemia has been associated with all NRTIs, especially after long durations of exposure.¹⁰²⁻¹⁰⁴ It appears that d4T-containing ART is an independent risk factor for the development of LA,¹⁰⁶ ddI-containing ART has also been implicated. Recently, it appears that concomitant use of ribavirin (RBV) and d4T/ddI places the patient at increased risk for LA development.¹⁰² Female patients, especially those who are pregnant, appear to be at greater risk of developing LA. Other risk factors include peripheral neuropathy and lipoatrophy, decreased bone mineral density, and obesity.¹⁰²⁻¹⁰⁴ Of note, a high proportion of patients with the HIV-associated neuromuscular weakness syndrome also have elevated lactate levels.¹⁰⁷

Pathogenesis. Although still under investigation, the pathogenesis of elevated lactate concentrations appears to be related to the inhibition of mitochondrial DNA (mtDNA) polymerase by NRTIs. The resulting decrease in mtDNA leads to impaired synthesis of proteins, especially those in the oxidative/phosphorylation system. If >70 percent reduction in mtDNA occurs, the metabolism becomes anaerobic with the resultant generation of lactic acid. Recent *in vitro* studies have suggested that PIs as well as NRTIs may result in mitochondrial damage.¹⁰⁸ In addition, other mechanisms may be operating; for example, ZDV appears to have direct toxicity on liver and muscle cells. In moderate to severe hyperlactatemia, the main target organ appears to be the liver.

Screening/diagnosis. Because the clinical features of hyperlactatemia are non-specific (eg, fatigue, malaise, weight loss, nausea and vomiting, dyspnea, myalgias, and abdominal bloating), routine measurements of lactate levels are NOT recommended. Instead, a keen awareness of possible potentiating factors and vigilance are necessary. Lactate levels should be measured immediately in those suspected of suffering from LA, as multi-organ failure leading to dysrhythmias, respiratory failure, coma, and death may ensue. With LA, hepatic dysfunction predominates; hypovolemia and sepsis, however, are not seen. Other causes of LA such as pancreatitis, dehydration, and acute hepatic failure from other causes must, as well as sepsis itself, of course, be ruled out.

Management. The mainstay of treatment is **immediate** cessation of NRTIs in all patients with confirmed lactate levels >10 mmol/L or symptomatic hyperlac-

tatemia with levels >5 mmol/L. The remainder of the ARV regimen should also be stopped so as not to promote ARV drug resistance. Care is supportive with regular monitoring of lactate levels; however, the frequency of monitoring is not clear. Lactate levels may remain elevated for weeks to months after the resolution of symptoms. While efficacy has not been proven, adjuvant therapy with a number of vitamin coenzymes (thiamine, riboflavin, and vitamin C), electron acceptors (coenzyme Q), and L-carnitine used in other mitochondrial diseases may be helpful and carry little risk.^{102,104}

Although it has been done successfully,¹⁰⁸ reinstatement of NRTI-containing ART is not generally recommended for LA in accord with current treatment guidelines.^{70,71} If NRTIs are deemed essential components when re-starting ART, NRTIs with less potential for mitochondrial toxicity such as ABC, 3TC/emtricitabine (FTC), and/or TDF should be used, and routine monitoring of lactate levels may be indicated.

Conclusions

The treatment of HIV infection has been complicated by short-term toxicities and long-term complications. The latter were initially referred to as the components of the "lipodystrophy syndrome." These complications are more accurately referred to as the morphologic and metabolic complications of HIV disease and ART. Although these complications have been well described and characterized, the mechanisms underlying their occurrence remain elusive. Guidelines exist for helping the clinician manage these complications. However, current guidelines are not particularly user-friendly for the busy HIV care provider.

This Advisory Committee has endeavored to outline the major morphologic and metabolic complications, as well as to provide the essentials of their management for the front-line HIV/AIDS-treating clinician. Knowing that HIV medicine is always a rapidly changing field, the Advisory Committee recognizes that the approaches to dealing with these complications not only remain somewhat unclear, but also are subject to revision at any time. Nevertheless, it is the Advisory Committee's hope that the above information and recommendations will assist clinicians in better managing these complications. ■

References

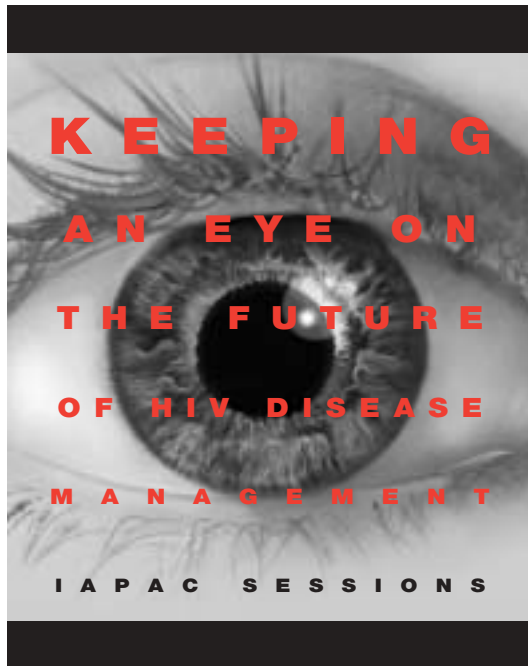
1. Mauss S, Corzilius M, Wolf E, et al. Risk factors for the HIV-associated lipodystrophy syndrome in a closed cohort of patients after 3 years of antiretroviral treatment. *HIV Med* 2002;3:49-55.
2. Mallon P, Miller J, Cooper D, Carr A. Prospective evaluation of the effects of antiretroviral therapy on body composition in HIV-1-infected men starting therapy. *AIDS* 2003;17:971-979.
3. Palella F, Jr., Cole S, Chmiel J, et al. Anthropometrics and examiner-reported body habitus abnormalities in the multicenter AIDS cohort study. *Clin Infect Dis* 2004;38:903-907.
4. Grunfeld C, Saag M, Shevitz A, van der Horst C, Currier J, Veronese F. Losses and gains: Insights from the preliminary results of the Fat Redistribution and Metabolic Changes in HIV Infection Study (FRAM). 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment; July 25, 2003; Paris. Unpublished data.
5. Lichtenstein K, Dlanev K, Armon C, et al. Incidence of and risk factors for lipodystrophy (abnormal fat loss) in ambulatory HIV-1-infected patients. *J Acquir Immune Defic Syndr* 2003;32:48-56.
6. Dubé M, Zackin R, Tebas P, et al. Prospective study of regional body composition in antiretroviral-naïve subjects randomized to receive zidovudine + lamivudine or didanosine + stavudine combined with nevirapine, efavirenz or both: A5005s, a substudy of ACTG 384. 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV. September 22-25, 2002. San Diego. [abstract 27]
7. Shlay J, Visnegarwala F, Bartsch, et al. Body composition and metabolic changes in antiretroviral-naïve HIV-infected patients randomized to didanosine and stavudine (ddl+d4T) vs. abacavir and lamivudine (ABC+3TC). XV International AIDS Conference. July 11-16, 2004. Bangkok. [abstract ThOrB1360]
8. Joly V, Flandre P, Meiffredy V, et al. Increased risk of lipodystrophy under stavudine in HIV-1-infected patients: Results of a substudy from a comparative trial. *AIDS* 2002;16:2447-2454.
9. Yeni P, Hammer S, Hirsch M, et al. Treatment for adult HIV infection: 2004 recommendations of the International AIDS Society-USA Panel. *JAMA* 2004;292:251-265.
10. Mallal S, John M, Moore C, et al. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. *AIDS* 2000;14:1309-1316.
11. Moyle G. Mitochondrial toxicity hypothesis for lipodystrophy: A refutation. *AIDS* 2001;15:413-415.
12. McComsey G, Paulsen D, Lonergan T, et al. Improvements in mitochondrial (mt) DNA levels after substituting ABC or ZDV for d4T in HIV-infected patients with lipodystrophy (LA). 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy. September 27-30, 2002. San Diego. [abstract H-1930]
13. Gallant J, Staszewski S, Pozniak A, et al. Favorable lipid and mitochondrial (mt) DNA profile for tenofovir disoproxil fumarate (TDF) compared to stavudine (d4T) in combination with lamivudine (3TC) and efavirenz (EFV) in antiretroviral therapy (ART) naïve patients: A 48 week interim analysis. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy. September 27-30, 2002. San Diego. [abstract LB-2]
14. Anderson P, Kakuda T, Lichtenstein K. The cellular pharmacology of nucleoside- and nucleotide-analogue reverse-transcriptase inhibitors and its relationship to clinical toxicities. *Clin Infect Dis* 2004;38:743-753.
15. Martin A, Smith D, Carr A, et al. Reversibility of lipodystrophy in HIV-infected patients 2 years after switching from thymidine analogue to abacavir: The MITOX Extension Study. *AIDS* 2004;18:1029-1036.
16. McComsey G, Ward D, Henthaler S, et al. Improvement in lipodystrophy associated with highly active antiretroviral therapy in human immunodeficiency virus-infected patients switched from stavudine to abacavir or zidovudine: The results of the TARHEEL study. *Clin Infect Dis* 2004;38:263-270.
17. Moyle G, Baldwin C, Langroudi B, Mandalia S, Gazzard BG. A 48-week, randomized open-label comparison of three abacavir-based substitution approaches in the management of dyslipidemia and peripheral lipodystrophy. *J Acquir Immune Defic Syndr* 2003;33:22-28.
18. Martinez E, Arnaiz J, Podzanczer D, et al. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. *N Engl J Med* 2003;349:1036-1046.
19. Carr A, Workman C, Carey D, et al. No effect of rosiglitazone for treatment of HIV-1 lipodystrophy: Randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;363:429-438.
20. Sutinen J, Hakkinen A, Westerbacka J, et al. Rosiglitazone in the treatment of HAART-associated lipodystrophy—A randomized double-blind placebo-controlled study. *Antivir Ther* 2003;8:199-207.
21. Hadigan C, Yawetz S, Thomas A, Havers F, Sax P, Grinspoon S. Metabolic effects of rosiglitazone in HIV lipodystrophy: A randomized, controlled trial. *Ann Intern Med* 2004;140:786-794.
22. Hadigan C, Corcoran C, Basgoz N, Davis B, Sax P, Grinspoon S. Metformin in the treatment of HIV lipodystrophy syndrome: A randomized controlled trial. *JAMA* 2000;284:472-477.
23. Guaraldi G, De Fazio D, Orlando G, et al. Autologous fat transfer for treating facial wasting in HIV body fat redistribution syndrome. 10th Conference on Retroviruses and Opportunistic Infections. February 10-14, 2003. Boston. [abstract 722]
24. Valantin M, Aubron-Olivier C, Ghosn J, et al. Polyactic acid implants (New-Fill™) to correct facial lipodystrophy in HIV-infected patients: Results of the open-label study VEGA. *AIDS* 2003;17:2471-247.
25. Moyle G, Lysakova L, Brown, et al. A randomized open-label study of immediate versus delayed polyactic acid injections for the cosmetic management of facial lipodystrophy with HIV infection. *HIV Med* 2004;5:82-87.
26. Lo JC, Mulligan K, Tai VW, Algren H, Schambelan M. "Buffalo hump" in men with HIV-1 infection. *Lancet* 1998;351:867-870.
27. Engelson EE, Kotler DP, Tan YX, Wang J, Pierson RN, Heymsfield SB. Fat distribution in HIV-infected patients reporting truncal enlargement quantified by whole-body magnetic resonance imaging. *Am J Clin Nutr* 1999;69:1162-1169.
28. Lichtenstein KA, Ward DJ, Moorman AC, et al. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. *AIDS* 2001;15:1389-1398.
29. Arpadi SM, Cuff PA, Horlick M, Wang J, Kotler DP. Lipodystrophy in HIV-infected children is associated with high viral load and low CD4+ lymphocyte count and CD4+ lymphocyte percent age at baseline and use of protease inhibitors and stavudine. *J Acquir Immune Defic Syndr* 2001;27:30-34.
30. Chang P, Kotler DP, Engelson ES, Kenley S, Muurhainen N, Gertner JM. Anthropometric equations distinguish between HIV+ subjects affected and unaffected with HIV-associated adipose redistribution syndrome (HARS). 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. September 17-20, 2000. Toronto. [abstract 1283]
31. Roubenoff R, Weiss L, McDermott A, et al. A pilot study of exercise training to reduce trunk fat in adults with HIV-associated fat redistribution. *AIDS* 1999;13:1373-1375.
32. Engelson ES, Glesby MJ, Mendez C, Albu JB, Wang J, Heymsfield SB, Kotler DP. Effect of recombinant human growth hormone in the treatment of visceral fat accumulation in HIV infection. *J Acquir Immune Defic Syndr* 2002;30:379-391.
33. Kotler DP, Muurhainen N, Grunfeld C, et al, and the STARS study group. Effects of growth hormone on abnormal visceral adipose tissue accumulation and dyslipidemia in HIV-infected patients. *J Acquir Immune Defic Syndr* 2004;35:239-254.
34. Hadigan C, Meigs J, Corcoran C, et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. *Clin Infect Dis* 2001;32:130-139.
35. Brown T, Cole S, Li X, et al. Prevalence and incidence of pre-diabetes and diabetes in the Multicenter AIDS Cohort Study. 11th Conference on Retroviruses and Opportunistic Infections. February 8-11, 2004. San Francisco. [abstract 73]
36. Klett A, Fultz S, Kwok C, Kelley D, Skanderson M, Justice A. Risk of diabetes in HIV infected veterans pre- and post-HAART and the role of HCV coinfection. *Hepatology* 2004;40:115-119.
37. Justman J, Benning L, Danoff A, et al. Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women. *J Acquir Immune Defic Syndr* 2003;32:298-302.
38. Mehta S, Brancati F, Sulkowski M, Strathdee S, Szklo M, Thomas D. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Ann Intern Med* 2000;133:592-599.
39. Mehta S, Moore R, Thomas D, Chaisson R, Sulkowski M. The effect of HAART and HCV infection on the development of hyperglycemia among HIV-infected persons. *J Acquir Immune Defic Syndr* 2003;33:577-584.
40. Friis-Moller N, Sabin C, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003;349:1993-2003.
41. Noor M, Lo J, Mulligan K, et al. Metabolic effects of indinavir in healthy HIV-seronegative men. *AIDS* 2001;15:F11-F18.
42. Mynarcik D, McNurlan M, Steigbigel R, Fuhrer J, Gelato M. Association of severe insulin resistance with both loss of limb fat and elevated serum tumor necrosis factor receptor levels in HIV lipodystrophy. *J Acquir Immune Defic Syndr* 2000;25:312-321.

43. Meininger G, Hadigan C, Rietschel P, Grinspoon S. Body-composition measurements as predictors of glucose and insulin abnormalities in HIV-positive men. *Am J Clin Nutr* 2002;76:460-465.
44. Saint-Marc T, Touraine J. Effects of metformin on insulin resistance and central adiposity in patients receiving effective protease inhibitor therapy. *AIDS* 1999;13:1000-1002.
45. Gelato M, Mynarcik D, Quick J, et al. Improved insulin sensitivity and body fat distribution in HIV-infected patients treated with rosiglitazone: A pilot study. *J Acquir Immune Defic Syndr* 2002;31:163-170.
46. Raskin P, Rappaport E, Cole S, Yan Y, Patwardhan R, Freed M. Rosiglitazone short-term monotherapy lowers fasting and post-prandial glucose in patients with type II diabetes. *Diabetologia* 2000;43:278-284.
47. Friis-Møller N, Weber R, D'Arminio Monforte A, et al. Exposure to HAART is associated with an increased risk of myocardial infarction: The D.A.D. Study. 10th Conference on Retroviruses and Opportunistic Infections. February 10-14, 2003. Boston. [abstract 130]
48. Holmberg S, Moorman A, Williamson J, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. *Lancet* 2002;360:1747-1748.
49. Rickerts V, Brodt H, Staszewski S, Stille W. Incidence of myocardial infarctions in HIV-infected patients between 1983 and 1998: The Frankfurt HIV-cohort study. *Eur J Med Res* 2000;5:329-333.
50. Moore R, Lucas G. Increasing incidence of cardiovascular disease in HIV-infected persons in care. 10th Conference on Retroviruses and Opportunistic Infections. February 10-14, 2003. Boston. [abstract 132]
51. Mary-Krause M, Cotte L, Simon A, et al. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. *AIDS* 2003;17:2479-2486.
52. Currier J, Taylor A, Boyd F, et al. Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr* 2003;33:506-512.
53. Klein D, Hurley L, Quesenberry C, Jr., Sidney S. Hospitalization for coronary heart disease and myocardial infarction among men with HIV-1 infections: Additional follow-up. 10th Conference on Retroviruses and Opportunistic Infections. February 10-14, 2003. Boston. [abstract 747]
54. Bozzette S, Ake C, Tam H, Chang S, Louis T. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. *N Engl J Med* 2003;348:702-710.
55. Riddler S, Smit E, Cole S, et al. Impact of HIV infection and HAART on serum lipids in men. *JAMA* 2003;289:2978-2982.
56. Purnell J, Zambon A, Knopp R, et al. Effect of ritonavir on lipids and post-heparin lipase activities in normal subjects. *AIDS* 2000;14:51-57.
57. Gallant J, Staszewski S, Pozniak A, et al. Efficacy and safety of tenofovir DF vs. stavudine in combination therapy in antiretroviral naive patients. *JAMA* 2004;292:191-201.
58. Domingo P, Labarga P, Llibre J, et al. Evolution of dyslipidemia in virologically suppressed HIV-infected patients switching from stavudine to tenofovir DF. 9th European AIDS Conference. October 26-29, 2003. Warsaw. [abstract F 8/5]
59. DeJesus E, Herrera G, Teofilo E, et al. Abacavir BID versus zidovudine BID in combination with 3TC and efavirenz in ART-naive subjects: CNA30024: 48 week final results. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy. September 14-17, 2003. Chicago. [abstract H-446]
60. van Leth F, Phanuphak P, Gazzard B, et al. Lipid changes in a randomized comparative trial of first-line antiretroviral therapy with regimens containing either nevirapine alone, efavirenz alone or both drugs combined, together with stavudine and lamivudine (2NN Study). 10th Conference on Retroviruses and Opportunistic Infections. February 10-14, 2003. Boston. [abstract 752]
61. Maggi P, Lillo A, Perilli F, et al. Colour-Doppler ultrasonography of carotid vessels in patients treated with antiretroviral therapy: A comparative study. *AIDS* 2004;18:1023-1028.
62. Hsue P, Lo J, Franklin A, et al. Progression of atherosclerosis as assessed by carotid intima-media thickness in HIV-infected patients. *Circulation* 2004;109:1603-1608.
63. Talwani R, Falusi O, Mendes de Leon C, et al. Electron beam computed tomography for assessment of coronary artery disease in HIV-infected men receiving antiretroviral therapy. *J Acquir Immune Defic Syndr* 2002;30:191-195.
64. Meng Q, Lima J, Lai H, et al. Coronary artery calcification, atherogenic lipid changes, and increased erythrocyte volume in black injection drug users infected with human immunodeficiency virus-1 treated with protease inhibitors. *Am Heart J* 2002;144:642-648.
65. Pierone G, Cho N, Mieras J, et al. Determination of subclinical atherosclerosis in patients on long-term nevirapine, efavirenz, and protease inhibitor-based antiretroviral therapy by ultrasound measurement of carotid artery intima-media thickness and multislice cardiac CT measurement of coronary artery calcium. Presented at XV International AIDS Conference. July 11-16, 2004. Bangkok. [abstract ThOrB1355]
66. Chimowitz M, Weiss D, Cohen S, et al. Cardiac prognosis of patients with carotid stenosis and no history of coronary artery disease. Veterans Affairs Cooperative Study Group 167. *Stroke* 1994;25:759-765.
67. O'Leary D, Polak J, Kronmal R, et al. Carotid-artery intimal and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med* 1999;340:14-22.
68. Smilde T, van Wissen S, Wollersheim H, et al. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): A prospective, randomised, double-blind trial. *Lancet* 2001;357:577-581.
69. Rumberger J, Simons D, Fitzpatrick L, Sheedy P, Schwartz R. Coronary artery calcium area by electron beam tomography and coronary atherosclerotic plaque area. *Circulation* 1995;92:2157-2162.
70. Dubé M, Stein J, Aberg J, et al, for the Adult AIDS Clinical Trials Group Cardiovascular Subcommittee. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: Recommendations of the HIV Medicine Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis* 2003;37:613-627.
71. Schambelan M, Benson C, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: Recommendations of an international AIDS Society-USA Panel. *J Acquir Immune Defic Syndr* 2002;31:257-275.
72. Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS). Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. March 23, 2004. Accessed October 25, 2004 at: <http://AIDSinfo.nih.gov>
73. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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.
74. Drechsler H, Powderly W. Switching effective antiretroviral therapy: A review. *Clin Infect Dis* 2002;35:1219-1230.
75. Haas D, Zala C, Schrader S, et al. Therapy with atazanavir plus saquinavir in patients failing highly active antiretroviral therapy: A randomized comparative pilot trial. *AIDS* 2003;17:1339-1349.
76. Stein E. The power of statins: Aggressive lipid lowering. *Clin Cardiol* 2003;26:25-31.
77. Carr R, Andre A, Bertz R, et al. Concomitant administration of ABT-378/ritonavir (ABT-378/R) results in a clinically important pharmacokinetic (PK) interaction with Atorvastatin (ATO) but not pravastatin. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. September 17-20, 2000. Toronto. [abstract 1644]
78. Fichtenbaum C. The evaluation and management of dyslipidemia in HIV-infected patients. *AIDS Clin Care* 2001;13:113-117, 120.
79. Fichtenbaum C, Gerber J, Rosenkranz S, et al. (NIAID AIDS Clinical Trials Group). Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. *AIDS* 2002;16:569-577.
80. Schuster H. Rosuvastatin—a highly effective new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor: Review of clinical trial data at 10-40 mg doses in dyslipidemic patients. *Cardiology* 2003;99:126-139.
81. Gerber J, Fichtenbaum C, Rosenkranz S, et al. Efavirenz (EFV) is a significant inducer of simvastatin (SIM) and atorvastatin (ATR) metabolism: Results of ACTG A5108 study. 11th Conference on Retroviruses and Opportunistic Infections. February 8-11, 2004. San Francisco. [abstract L-3]
82. Jau L, Cheng J. Pharmacology and therapeutics of ezetimibe (SCH 58235), a cholesterol-absorption inhibitor. *Clin Ther* 2003;25:2352-2387.
83. Calza L, Manfredi R, Chiodo F. Dyslipidemia associated with antiretroviral therapy in HIV-infected patients. *J Antimicrobial Chemotherapy* 2004;53:10-14.
84. Aberg J, Zackin R, Evans S, et al, and ACTG 5087 team. A prospective, multicenter, randomized trial comparing the efficacy and safety of fenofibrate (F) versus pravastatin (P) in HIV-infected subjects with lipid abnormalities: Final results of ACTG 5087. 11th Conference on Retroviruses and Opportunistic Infections. February 8-11, 2004. San Francisco. [abstract N-53]
85. Gerber M, Yarasheski K, Drechsler H, et al. Niacin in HIV-infected individuals with hyperlipidemia receiving potent antiretroviral therapy. 10th Conference on Retroviruses and Opportunistic Infections. February 10-14, 2004. Boston. [abstract 726]
86. Wohl D, Cunningham C, Tien H-C, et al. A randomized open label clinical trial of omega-3 fatty acid (fish oil) supplementation along with diet and exercise in HIV-infected patients with hypertriglyceridemia. 11th Conference on Retroviruses and Opportunistic Infections. February 8-11, 2004. San Francisco. [abstract 724]
87. Moyle G, 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.
88. Henry K, Melroe H, Huebesch J, et al. Atorvastatin and gemfibrozil for protease-inhibitor-related lipid abnormalities. *Lancet* 1998;352:1031-1032.
89. Hewitt R, Shelton M, Esch L. Gemfibrozil effectively lowers protease inhibitor-associated hypertriglyceridemia in HIV-1-positive patients. *AIDS* 1999;13:868-869.
90. Manfredi R, Calza L, Chiodo F. Statins and fibrates for the treatment of hyperlipidemia in HIV-infected patients receiving HAART. *AIDS* 2003;17:851-859.
91. Caramelli B, de Bernoche C, Sartori A, et al. Hyperlipidemia related to the use of HIV-protease inhibitors: Natural history and results of treatment with fenofibrate. *Braz J Infect Dis* 2001;5:332-338.
92. Osteoporosis prevention, diagnosis, and therapy. NIH Consensus Statement 2000; 17:1-45.
93. Miller K, Masur H, Jones E, et al. High prevalence of osteonecrosis of the femoral head in HIV-infected adults. *Ann Intern Med* 2002;137:17-25.
94. McGowan I, Cheng A, Coleman S, Johnson A, Genant H. Assessment of bone mineral density (BMD) in HIV-infected antiretroviral-therapy-naive patients. 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001. Chicago. [abstract 628]
95. Tebas P, Powderly W, Claxton S, et al. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. *AIDS* 2000;14:F63-F67.
96. Hoy J, Hudson J, Law M, Cooper D. Osteopenia in a randomized, multicenter study of protease inhibitor (PI) substitution in patients with the lipodystrophy syndrome and well-controlled HIV viremia. 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000. San Francisco. [abstract 208]
97. Mondy K, Lassa-Claxton S, Hoffmann M, Yarasheski K, Powderly W, Tebas P. Longitudinal evolution of bone mineral density (BMD) and bone markers in HIV-infected individuals. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle. [abstract 718-T]
98. Knobel H, Guelar A, Vallecillo G, Noguez X, Diez A. Osteopenia in HIV-infected patients: Is it the disease or is it the treatment? *AIDS* 2001;15:807-808.
99. Carr A, Miller J, Eisman J, Cooper D. Osteopenia in HIV-infected men: Association with asymptomatic lactic acidemia and lower weight pre-antiretroviral therapy. *AIDS* 2001;15:703-709.
100. Mondy K, Powderly W, Claxton S, Yarasheski K, Stoneman J, Tebas P. Alendronate, vitamin D and calcium for the treatment of osteopenia/osteoporosis associated with HIV infection. 10th Conference on Retroviruses and Opportunistic Infections. February 10-14, 2003. Boston. [abstract 134]
101. Bruera D, Luna N, David D, Bergoglio L, Zamudio J. Decreased bone mineral density in HIV-infected patients is independent of antiretroviral therapy. *AIDS* 2003;17:1917-1923.
102. Falco V, Crespo M, Ribera E. Lactic acidosis related to nucleoside therapy in HIV-infected patients. *Expert Opin Pharmacother* 2003;4:1321-1329.
103. Arenas-Pinto A, Grant A, Weller I. Lactic acidosis in HIV infected patients: A systematic review of published cases. *Sex Transm Infect* 2003;79:340-344.
104. Carr A. Lactic acidemia in infection with Human Immunodeficiency Virus. *Clin Infect Dis* 2003;36:S96-100.
105. Wohl D, Pilcher C, Evans S, et al. Absence of sustained hyperlactatemia in HIV-infected patients with risk factors for mitochondrial toxicity. *J Acquir Immune Defic Syndr* 2004;35:274-278.
106. Datta D, Moyle G, Mandelia S, Gazzard B. Matched case-control study to evaluate risk factors for hyperlactatemia in HIV patients on antiretroviral therapy. *HIV Med* 2003;4:311-314.
107. HIV Neuromuscular Syndrome Study Group. HIV-associated neuromuscular weakness syndrome. *AIDS* 2004;18:1403-1412.
108. Nerurkar P, Pearson L, Frank J, et al. Highly active antiretroviral therapy (HAART)-associated lactic acidosis: *in vitro* effects of combination of nucleoside analogues and protease inhibitors on mitochondrial function and lactic acid production. *Cell Mol Biol* 2003;49:1205-1211.



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ABSTRACTS

New England Journal of Medicine

Expanded screening for HIV in the United States: An analysis of cost effectiveness

Paltiel AD, Weinstein MC, Kimmel AD, et al.

BACKGROUND: Roughly 280,000 Americans are unaware of their human immunodeficiency virus (HIV) infection. The effect of expanded screening for HIV is unknown in the era of effective antiretroviral therapy. **METHODS:** We developed a computer simulation model of HIV screening and treatment to compare routine, voluntary HIV counseling, testing, and referral (HIVCTR) with current practice in three target populations: "high risk" (3.0 percent prevalence of undiagnosed HIV infection; 1.2 percent annual incidence); "CDC threshold" (1.0 percent and 0.12 percent, respectively); and "US general" (0.1 percent and 0.01 percent). Input data were derived from clinical trials and observational cohorts. Outcomes included quality-adjusted survival, cost, and cost effectiveness. **RESULTS:** In the high-risk population, the addition of one-time screening for HIV antibodies with an enzyme-linked immunosorbent assay (ELISA) to current practice was associated with earlier diagnosis of HIV (mean CD4 count at diagnosis, 210 versus 154/mm³). One-time screening also improved average survival time among HIV-infected patients (quality-adjusted survival, 220.7 months versus 219.8 months). The incremental cost effectiveness was US\$36,000 per quality-adjusted life-year gained. Testing every five years cost US\$50,000 per quality-adjusted life-year gained, and testing every three years cost US\$63,000 per quality-adjusted life-year gained. In the CDC threshold population, the cost-effectiveness ratio for one-time screening with ELISA was US\$38,000 per quality-adjusted life-year gained, whereas testing every five years cost US\$71,000 per quality-adjusted life-year gained, and testing every three years cost US\$85,000 per quality-adjusted life-year gained. In the US general population, one-time screening cost US\$113,000 per quality-adjusted life-year gained. **CONCLUSIONS:** In all but the lowest-risk populations, routine, voluntary screening for HIV once every three to five years is justified on both clinical and cost-effectiveness grounds. One-time screening in the general population may also be cost-effective.

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Journal of the American Medical Association

Intermittent HIV-1 viremia (blips) and drug resistance in patients receiving HAART

Nettles RE, Kieffer TL, Kwon P, et al.

OBJECTIVE: To test the hypothesis that blips represent random biological and statistical variation around mean steady-state HIV-1 RNA levels slightly below 50 copies/mL rather than biologically significant elevations in viremia. **DESIGN, SETTING, AND**

PATIENTS: Between June 19, 2003, and February 9, 2004, patients receiving therapy underwent intensive sampling (every two to three days) over three to four months to define the frequency, magnitude, and duration of blips and their association with drug levels and other clinical variables. Blips were defined as HIV-1 RNA measurements greater than or equal to 50 copies/mL preceded and followed by measurements less than 50 copies/mL without a change in treatment. To determine whether blips result from or lead to drug resistance, an ultrasensitive genotyping assay was used to detect drug resistance mutations before, during, and after blips. Patients were 10 HIV-1-infected asymptomatic adults recruited by clinicians and followed up in the Moore Clinic at the Johns Hopkins Hospital. Patients had suppression of viremia to below 50 copies/mL while receiving a stable antiretroviral regimen for six months or longer. **RESULTS:** With the intensive sampling, blips were detected in nine of 10 patients. Statistical analysis was consistent with random assay variation around a mean viral load below 50 copies/mL. Blips were not concordant on independent testing and had a short duration (median, less than three days) and low magnitude (median, 79 copies/mL). Blip frequency was not associated with demographic, clinical, or treatment variables. Blips did not occur in relation to illness, vaccination, or directly measured antiretroviral drug concentrations. Blips were marginally associated ($p = 0.08$) with reported episodes of non-adherence. Most importantly, in approximately 1,000 independent clones sequenced for both protease and reverse transcriptase, no new resistance mutations were seen before, during, or shortly after blips. **CONCLUSION:** Most blips in this population appear to represent random biological and statistical variation around mean HIV-1 levels below 50 copies/mL rather than clinically significant elevations in viremia.

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American Journal of Gastroenterology

The effect of HIV coinfection on the risk of cirrhosis and hepatocellular carcinoma in US veterans with hepatitis C

Kramer JR, Giordano TP, Souček J, et al.

OBJECTIVES: This study was conducted to determine whether HIV coinfection increases the risk of cirrhosis in HCV-infected patients in the HAART and pre-HAART eras. Further, the risk of hepatocellular carcinoma was also examined. **METHODS:** This retrospective cohort study was conducted among HCV-infected veterans who were seen at one of the 172 Veterans Health Administration hospitals between October 1, 1991, and September 30, 2000. Patients with prerecorded advanced liver disease were excluded. Incidence rates, cumulative incidence, and Cox proportional hazard ratios were calculated. **RESULTS:** There were 26,641 patients with HCV

only and 4,761 patients with HCV/HIV coinfection. The unadjusted incidence rate of cirrhosis was lower in patients with coinfection than in those with HCV only ($p < 0.01$). After controlling for demographics and confounders (including alcoholism and chronic hepatitis B), coinfection was not significantly associated with cirrhosis. However, there was an increased risk of cirrhosis in patients with coinfection compared to patients with HCV only during the pre-HAART era (before October 1, 1996) (hazard ratio = 1.48, CI 1.06-2.07, $p = 0.02$), but not among patients who entered the cohort during the HAART era. The unadjusted incidence rate of hepatocellular carcinoma in patients with coinfection and with HCV only was 1.3 and 2/1,000 person-years, respectively ($p = 0.04$). In the multivariate model, coinfection was not associated with hepatocellular carcinoma (hazard ratio = 0.84, $p = 0.40$). **CONCLUSIONS:** Coinfection was a significant risk factor for cirrhosis only during the pre-HAART era and was not associated with hepatocellular carcinoma, irrespective of time period.

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Journal of Infectious Diseases

Didanosine in HIV-1-infected patients experiencing failure of antiretroviral therapy: A randomized placebo-controlled trial

Molina JM, Marcelin AG, Pavie J, et al.

BACKGROUND: The antiviral efficacy of didanosine in patients experiencing virological failure is not well known. **METHODS:** A total of 168 patients (139 men and 29 women) receiving stable antiretroviral therapy with plasma human immunodeficiency virus type 1 (HIV-1) RNA levels of 1,000 to 100,000 copies/mL were randomly assigned to have didanosine ($n = 111$) or placebo ($n = 57$) added to their currently failing regimen for four weeks. The primary efficacy endpoint was the change in HIV-1 RNA level from baseline to week 4. **RESULTS:** At baseline, the median HIV-1 RNA level was 3.8 log₁₀ copies/mL, the median CD4 count was 378 cells/mm³, and the median number of nucleoside reverse transcriptase inhibitor-associated mutations (NAMs) was four. At week 4, a significant decrease in the median HIV-1 RNA level was observed in the didanosine group, compared with that in the placebo group (-0.56 versus +0.07 log₁₀ copies/mL, respectively) ($p < 0.0001$). A total of 33 patients (31 percent) in the didanosine group, compared with three (6 percent) in the placebo group, had HIV-1 RNA levels <400 copies/mL ($p < 0.001$). Significant antiviral activity of didanosine was observed in patients with up to five NAMs at baseline. Diarrhea occurred in five patients (5 percent) in the didanosine group and two patients (4 percent) in the placebo group. **CONCLUSIONS:** In HIV-1-infected patients experiencing failure of antiretroviral therapy, didanosine retains short-term antiviral activity.

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The Evolution of ARV Therapy: Applying Clinical Trial Data to Optimize HAART in HIV Management

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- ✓ State recommendations for the timing of initial antiretroviral therapy for the treatment of adults and adolescents with HIV according to nationally recognized guidelines

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Does GB virus C protect against HIV disease progression?

Chris Gadd

Coinfection with hepatitis G (or GB virus C) may not be a protective factor in the progression of HIV disease, according to a longitudinal study presented in next month's edition of the *Journal of Infectious Diseases*.¹ The study found that loss of the virus was associated with faster progression and decreases in CD4 count, leading the authors to suggest that HIV disease progression may be a cause, not a consequence, of the loss of GB virus C.

GB virus C is a harmless virus that is closely related to hepatitis C virus (HCV). A number of studies have suggested that coinfection with this virus and HIV leads to slower HIV disease progression. However, this effect remains controversial, as not all studies have agreed with this conclusion, possibly due to differences in the length of HIV infection, definitions of GB virus C "infection" and other factors.

In an attempt to clarify the relationship between the two viruses, investigators from the Amsterdam Cohort Study carried out a large prospective study of 326 gay men, whose date of HIV seroconversion could be accurately estimated. This design allowed the researchers to assess the dynamics of GB virus C infection over time, and to compare this with the time of HIV seroconversion.

"Rather than a positive effect of GB virus C presence, a negative effect of GB virus C RNA loss on HIV-1 disease progression was found, which disappeared after adjustment for time-updated CD4 count," the authors conclude. "We therefore [hypothesize] that GB virus C RNA persistence depends on the presence of a sufficient number of CD4 cells, and that the CD4 cell decrease associated with HIV-1 disease progression is a cause, not a consequence, of GB virus C RNA loss."

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In addition to three monthly measurements of HIV viral load and CD4 counts, the investigators assessed GB virus C infection by testing the blood samples taken shortly after HIV seroconversion and again before January 1996. They tested for active GB virus C infection by measuring RNA levels using the polymerase chain reaction (PCR). Past infection with GB virus C was assessed by testing the samples for the presence of antibodies against the virus's envelope protein-2 (E2).

The men were followed up for a median of eight years. All of the men seroconverted before 1996, or had entered the study between October 1984 and May 1985, after having become infected with HIV.

In the first sample, 137 (42 percent) of the men tested positive for GB virus C RNA, and 134 (41 percent) had antibodies against E2. In the last sample, these values had decreased to 69 (21 percent) and 126 (39 percent) of the men, respectively.

Men with active GB virus C when the first sample was taken had a marginally increased risk of progression to a CD4 count <200 cells/mm³ (hazard ratio [HR] = 1.59; 95 percent confidence interval [CI]: 1.21 to 2.10), AIDS (HR = 1.37; 95 percent CI: 1.02 to 1.81) or death (HR = 1.44; 95 percent CI: 1.06 to 1.96).

This effect was unaffected by adjustment for age at seroconversion, CCR5 co-receptor genotype, antiretroviral therapy, or CD4 count or HIV viral load one year after seroconversion. However, when the change in CD4 cell counts across the follow-up period were taken into account, the effect of GB virus C RNA presence disappeared.

The presence of GB virus C antibodies did not have a significant effect on disease progression. There were also no significant differences in HIV disease progression between the men with active GB virus C infection, those with past infection, and those with no evidence of active or past infection.

"We found no evidence that GB virus C RNA or E2 antibodies had a protective effect

with regard to HIV-1 disease progression," the authors conclude.

In contrast, the 78 men who had GB virus C RNA at the first sample, but who had lost it by the last sample were more likely to experience progression to AIDS than those who never had the infection (HR = 2.91; 95 percent CI: 1.93 – 4.40). Similarly, the time of the first CD4 count <200 cells/mm³ was earlier, and survival was reduced in this group of men.

However, when the researchers adjusted their analysis to take CD4 cell counts into account, they saw that the effect of GB virus C RNA loss became much smaller. This suggests that CD4 count is associated with the loss of active GB virus C.

"GB virus C RNA loss was associated with more progressive HIV-1 disease, irrespective of the endpoint of the analysis," they comment. "This effect seemed to correlate most with changes in CD4 count, because the effect became weaker in multivariate analyses in which adjustment was made for this covariate. Because GB virus C RNA can replicate in CD4 cells, the decrease in CD4 cells during the course of HIV-1 infection implies a loss of target cells for GB virus C RNA. This might explain why GB virus C RNA loss is associated with an increased risk of death in HIV-1 infected individuals."

To test the robustness of their conclusions, the researchers repeated their analysis only using data from before the advent of highly active antiretroviral therapy (HAART) in 1996, to exclude any effect of effective antiretroviral therapy. This did not affect their findings. Similarly, neither restricting their analysis to only those patients whose date of seroconversion was accurately known nor adjusting their estimated times of GB virus C RNA loss affected their conclusions. ■

References

1. Van der Bij AK, Kloosterboer N, Prins M, et al. GB virus C coinfection and HIV-1 disease progression: The Amsterdam Cohort Study. *J Infect Dis* 2005;191:678-685.



IN THE LIFE



Mario E.A.F. Alves

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

This month, *IAPAC Monthly* is proud to feature Mario E.A.F. Alves, Clinical Professor/Director of the University of Illinois at Chicago HIV-AIDS Dental Program, in Chicago, Illinois.

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

"What is the use of living if it be not to strive for noble causes and to make this muddled world a better place for those who will live in it after we are gone?"
—Winston Churchill

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

My hobbies are photography and target shooting. My hidden talent would be fixing things.

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

I would live in Portugal, on the Algarve coast.

Who are your mentors or real life heroes?

My real life hero and mentor would be my father. He gave his children the example of success in life through honest and hard work, with responsibility and dignity.

With what historical figure do you most identify?

Michelangelo, for his achievements in many fields and his vision of the future.

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

Author: Luis de Camões. Painter: Vincent van Gogh. Composer: Frederic Chopin.

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

I am happy living in the current time period. History repeats itself.

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

I am very proud of being a dentist.

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

Greatest achievement: Computers. Greatest failure: World Wars I and II.

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

Not too different from what we have now. ■

An ounce of prevention



**Counsel your
HIV-positive
patients about
safer sex.**

**An ounce
of prevention
is worth
everyone's
effort!**



battling complacency
advancing commitment



SAY ANYTHING



It's a disturbing trend.

US National Center for Health Statistics researcher Geraldine McQuillan as quoted in a February 26, 2005, Washington Post article entitled, "US Survey Indicates Blacks Hardest Hit by HIV Infection." According to the US Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey, the government's most detailed study of Americans' health, HIV prevalence among African Americans doubled in the last decade, while remaining level among whites. In 1991, HIV prevalence in African Americans aged 18 to 59 was 1.1 percent, about five times greater than that found in whites. By 2001, it was 2.14 percent – 13 times that seen in whites. The study found that hardest hit were African-American men aged 40 to 49, 3.6 percent of whom were HIV-infected. McQuillan presented the findings at this year's 12th Conference on Retroviruses and Opportunistic Infections (CROI) in Boston



I am going to urge our government to involve us HIV-positive people in work on HIV/AIDS, especially in hospitals, because... we know how it is to live with HIV/AIDS.

Cynthia Leshomo, a 22-year-old AIDS counselor in Botswana, as quoted in a February 26, 2005, Associated Press report about that country's third annual Miss HIV Stigma Free pageant, a beauty pageant for HIV-positive women. Leshomo was crowned the winner in front of a crowd of about 500 onlookers, as well as a national audience of television viewers to whom the pageant was broadcast by state-owned television.



It's high time we move from concern to action in order to combat HIV/AIDS before it claims more lives. The most important thing to do is not to wait until we are in a dangerous situation and then do something.

Hind Khattab, an Egyptian public health expert, speaking at a February 2005 conference cosponsored by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and Jordan's Ministry of Health, during which health experts urged Middle Eastern and North African countries to enhance sex education and AIDS prevention interventions in schools to

curb an increase in HIV infections among the region's women and girls. More than 100 participants from 21 Arab countries attended the conference, which was the region's first to address HIV among females—a socially taboo topic in this traditional, religiously conservative region. Participants stated that womens' inability to negotiate safer sex, and their fear of coming forward due to stigma, is causing HIV to spread more rapidly throughout the region. UNAIDS estimates show there are 540,000 HIV-infected adults and children in the region; 92,000 new HIV infections occurred last year, up from 72,000 in 2002.




Being in a sex club for 36 hours on crystal meth and engaging in unprotected anal sex is really the most profound effect.

Steve Shoptaw, a research psychologist at the University of California, Los Angeles (UCLA) Integrated Substance Abuse Program, as quoted in a February 22, 2005, New York Times article entitled, "Scientists Explore Meth's Role in Immune System."

Crystal methamphetamine's effect on the immune system, HIV's progression, and the overall AIDS epidemic is receiving fresh scrutiny after New York City health officials reported that a crystal methamphetamine-using resident acquired multiple drug-resistant HIV and quickly progressed to AIDS. Experts fear more people, especially gay men, are using the drug—in many cases, with Viagra—to engage in unprotected sex with multiple partners. In the Explore Project, a long-term study of more than 4,000 gay men sexually active with more than one partner, researchers found a quarter of the men had tried crystal methamphetamine in the previous six months. All the crystal methamphetamine users were HIV-negative at the study's start, but by the end, about 2.1 percent had seroconverted. Independent of behaviors such as unprotected sex with multiple partners—which was strongly associated with infection—and injection drug use, men reporting crystal methamphetamine use were twice as likely to contract HIV.

WHY DOES KEVIN BACON WEAR THE BRACELET?

He wears it to raise desperately needed funds for HIV/AIDS care services, education and vaccine development. Over half a million people have chosen to wear The Bracelet. What about you? Available at: The Body Shop; Kenneth Cole; Virgin Megastore; Ben Bridge Jewelers and other fine retailers. Or visit us at WWW.UNTIL.ORG or call 1-800-88-UNTIL to order. 

Purchasing a UTAC bracelet contributes directly to the International Association of Physicians in AIDS Care (IAPAC) and its mission to improve access to quality treatment for all people living with HIV/AIDS. A full 25 percent of the price of each bracelet goes directly to IAPAC programming. Please be sure to mention IAPAC when shopping at www.until.org.