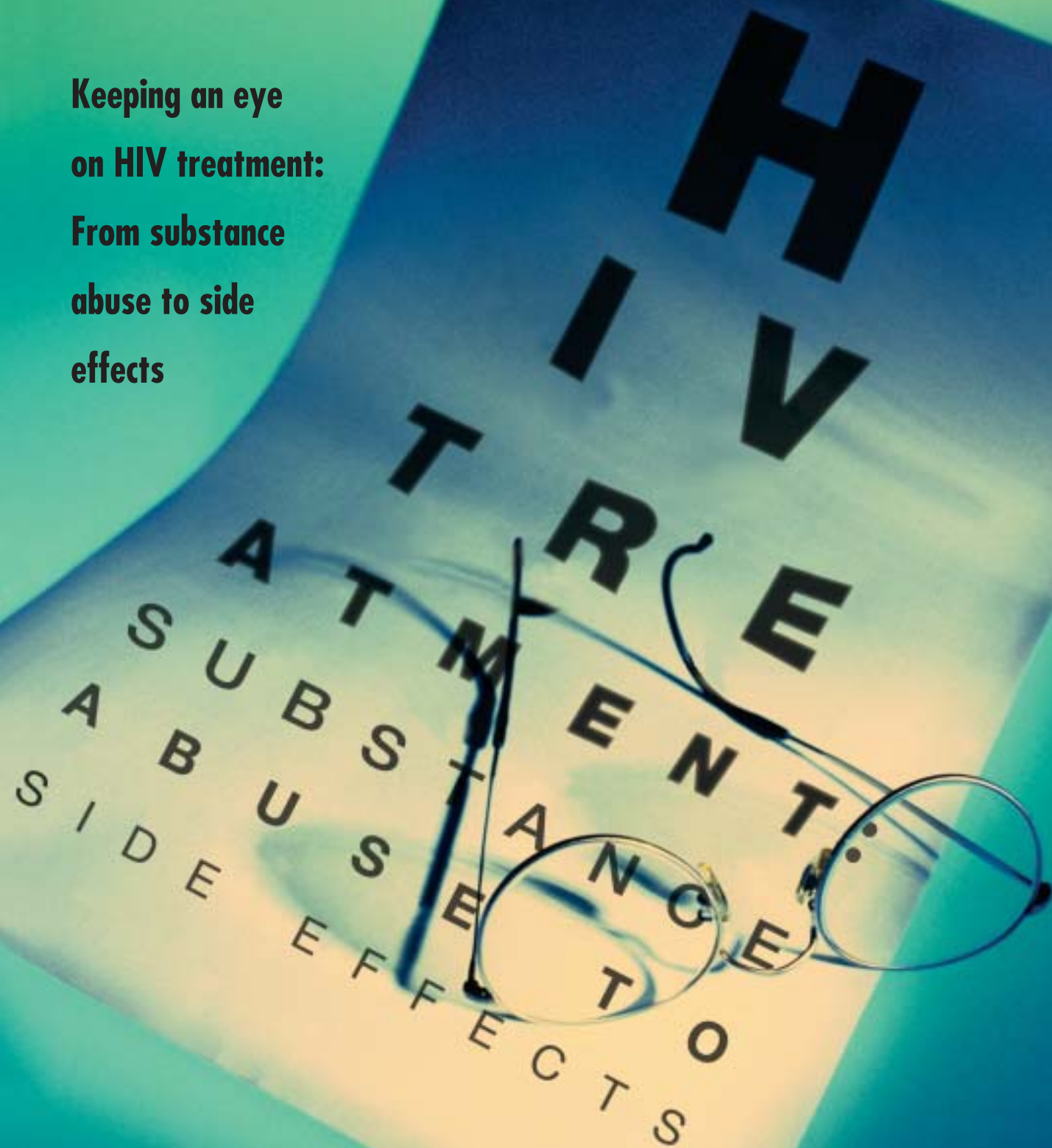


IAPAC

MONTHLY

**Keeping an eye
on HIV treatment:
From substance
abuse to side
effects**



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Keeping an eye on HIV treatment: From substance abuse to side effects

Mark Mascolini



The IAPAC Sessions 2003 spanned a panoply of problems facing HIV clinicians. This focused, two-day look at HIV medicine's challenges suggests that clinicians must have more than a little facility with everything from mental health to cell biology. Or at least they have to know what questions to ask and where to find answers.

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Shaping the future of the pandemic

José M. Zuniga

It is often said, rightly, that the AIDS pandemic is a matter of world-historical proportion. For centuries to come society will remember how our present crisis develops and recall the actions of this planet's inhabitants. Will historians look back to a time of blossoming global cooperation and compassion that set a new standard for human rights? Or will they see a period of preventable death and suffering on an unprecedented scale?

In the midst of such a moment of historical flux, there is a cloud of uncertainty through which it is difficult to discern the relative importance of any one event. Whether or not a development will greatly affect the overall outcome is difficult to judge, even when it seems at the time to clearly portend change.

I was thinking about all this as I sat on a Tuesday afternoon, May 27, 2003, in the US State Department's Acheson Auditorium. I had been invited by the White House for US President George W. Bush's signing of the Emergency Plan for AIDS Relief, and was honored, as I believe that the plan, which approves spending of up to US\$15 billion over five years, has the potential to create a significant shift in the global fight against HIV/AIDS.

The International Association of Physicians in AIDS Care (IAPAC) came out opposed to certain amendments and provisions that appeared in the final version of the legislation, but the plan as a whole, if it is followed through and if it sparks greater commitment from other world powers, is action of the type, and much nearer to the scale, that AIDS advocates have long called for. One must give credit where it is due.

In the immediate aftermath of fresh US funding pledges, however, we have not seen the world community unite in new ways to battle HIV/AIDS. Indeed, meeting shortly after President Bush's signing, the



leaders of the G8 countries, with the exceptions of France and the United Kingdom, failed to make any significant new pledges of funding. We may hope, as a next sign of commitment, that the European Union will indeed on June 26, 2003, at its annual bloc summit—only a few days from now, as I draft this report—commit to the US\$1 billion pledge to which it has recently hinted.

For now, need continues to greatly outweigh response, and the future of this disease and the efforts against it might seem as cloudy as ever.

The good news, though, is that we are not limited to simply watching events unfold. In the middle of an historic moment, we may lack the benefit of hindsight, with which we could clearly view how events transpire, but we are fortunate in that we have agency to shape the events themselves.

With that in mind, and in light of the planned US funding, this seems an appropriate occasion to discuss the ambitious

and varied work that IAPAC is undertaking. The IAPAC membership and staff, I know, are committed to turning every ounce of new momentum into real gains on behalf of humane medical treatment for all who suffer. We cannot let this moment pass; we cannot afford more good intentions that come to naught.

Medical education

Efforts to provide HIV-treating medications where they are lacking, along with proper medical infrastructure, must be a top priority. However, as these drugs become more widely available in resource-limited settings, and as prescribing and treating with them becomes increasingly complex in every setting, it is also crucial that we disseminate knowledge that can help physicians and allied healthcare professionals to properly employ these drugs and better care for their patients.

We feel this aspect of improving and equalizing treatment around the world has been given far too little attention. There may be concern that addressing potential difficulties is a poor advocacy strategy because these difficulties could be taken as an excuse not to expand the availability of needed drugs in developing countries. This is the wrong outlook to take. Rather, we must face our potential pitfalls head on and see them not as justifications for inaction, but as cause to act with yet greater effort and determination.

With this philosophy in mind, IAPAC has established a niche as an association working to improve HIV medicine by arming physicians and allied healthcare professionals with the treatment information they need.

Our two flagship publications provide valuable, up-to-date treatment information to their readers—and we are continually working to improve them. *IAPAC Monthly* has long been a valued resource for HIV

treatment providers owing largely to its in-depth coverage of clinical conferences. *JIAPAC* has, in a relatively short time, established itself as a source for original, peer-reviewed research and commentary, and I encourage our clinician members to engage this recently indexed journal as a vehicle through which to present research. For both publications, we have committed to increasing the amount of content that is relevant to developing world settings—an area of focus that is not well addressed in many other publications.

In the United States, we have distributed 90,000 sets of our GRIP Guides, which we know to be valuable to physicians in improving patients' adherence to complex drug regimens. Our antiretroviral therapy poster, which we have delivered after each iteration of the US Department of Health and Human Services' HIV treatment guidelines since 1996, is a tool for advancing appropriate prescribing practices. Other recent medical education materials include a supplement to *JIAPAC* examining the mental health complications associated with HIV and HIV-treating medications and succinct guides on this topic for patients and physicians.

With the opening of our first IAPAC Technical Annex in Geneva, under the leadership of Vice President/Chief Medical Officer Basil P. Vareldzis, we are set to introduce GRIP Guides and other HIV care tools, based on European treatment guidelines, to physicians and patients who need them in Europe.

IAPAC's African medical education materials include guides to information on major opportunistic infections, published in cooperation with Pfizer's Diflucan Partnership Program (DPP), that IAPAC's African Regional Office (IAPAC-AFRO, led by its Executive Director, Mulamba Diese) has translated into a dozen African languages. Drawing on the initiative and leadership of our members, we hope to expand the variety of materials and make them available in other resource-limited settings—much as we are drawing on our experience with US medical education materials as we adapt or develop them for Europe.

Technical assistance

IAPAC's technical assistance efforts are related to those in medical education in that they are designed to build the medical community's capacity to treat HIV-positive patients. We make the distinction that

technical assistance involves direct work with healthcare professionals and their patients while medical education is simply the distribution of clinical information.

Training programs have thus far made up the bulk of IAPAC's technical assistance work and, as with so many of our initiatives, it is set to increase dramatically. As the sole training provider in Africa for the DPP, IAPAC has reached over 12,000 physicians, nurses, pharmacists, laboratory technicians, and other health professionals in countries throughout southern, central, and eastern Africa.

At the request of trainees, the IAPAC-AFRO staff has begun including materials relating to antiretroviral treatment from our Global AIDS Learning & Evaluation Network (GALEN) curriculum in their training activities. The results have been positive, and it is a sign of good things to come from GALEN, whose compendium of learning modules is in rapid development. Work on GALEN's certification component is also advancing apace, enabling us to hold the first trial run of the GALEN examination at the 2nd IAS Conference on HIV Pathogenesis and Treatment in Paris. A systematic program of learning and certification is sorely needed to ensure appropriate HIV treatment around the world, and, in meeting this need, we are pleased to be working with respected international physicians to create and implement GALEN.

Another proven US program that IAPAC is working to establish in other areas of the world is the IAPAC Sessions. For the past three years, the association has convened 100 of its US members in Chicago for a program of short presentations followed by frank discussion and debate of the ongoing treatment challenges they face in their practices. The results have been very positive. In distinction from the limited dialogue afforded by the traditional conference format, physicians tell us that they benefit greatly from learning with and from their peers in this open forum. In consequence, and in response to demand, the IAPAC staff is working to bring this model to other countries and regions of the world.

We are already bringing together physicians and allied healthcare professionals around the world through IAPAC's I-Med Exchange. Originally limited to Africa, this program of thrice-monthly Internet conferences consists of top HIV-treating physicians presenting clinical information

in real time, with data-rich slide sets and audio. Participants from around the world take part and address questions and comments to presenters and colleagues.

Care provision

An estimated 800,000 of the world's 42 million people with HIV are currently receiving antiretroviral therapy. It is critically important for IAPAC to build professional capacity to deliver HIV care, including antiretroviral therapy. Yet, if the World Health Organization's goal of having 3 million people on antiretroviral therapy by the year 2005 is to become reality, IAPAC and other institutions must move beyond pilot antiretroviral drug access initiatives and advance substantial antiretroviral therapy scale-up efforts. In this respect, IAPAC is developing an HIV care provision agenda patterned after several models—including private sector partnerships and a franchise formula. Our association's goal is to establish clinical facilities whereby the provision of care, training, and research is facilitated in select geographical regions where political will and, as important, financial and human resources are existing.

IAPAC-AFRO is already collaborating with private sector mining interests around the establishment of company-sponsored antiretroviral therapy programs to benefit heavily HIV-affected mining company employee populations in several southern African countries. And, IAPAC staff in Chicago, Geneva, and Johannesburg are in the process of developing a franchise formula through which the association and our partners will create a network of health centers—sustained via collaborations between donors, governments, and institutional/individual stakeholders within various regions.

Through these important initiatives, IAPAC hopes to make real the expansion of access to HIV care and support to woefully underserved populations. Opening such facilities also will allow us to increase IAPAC's presence in the most HIV-affected regions of the world and, subsequently, provide much-needed support to healthcare professionals in those regions.

Advocacy

This broad agenda can be achieved if IAPAC is able to both draw upon and further motivate the commitment of like-minded individuals, partner organizations, and the

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IAPAC opens Technical Annex in Geneva

Former WHO Medical Officer appointed Vice President/Chief Medical Officer

Public health experts agree that, among other HIV treatment-related activities needed in the developing world, a tremendous effort must be made to train and support physicians and allied health-care professionals in HIV care.

Furthering its work in this area, the International Association of Physicians in AIDS Care (IAPAC) opened June 2, 2003, its IAPAC Technical Annex in Geneva, from which international medical education, capacity building, and technical assistance activities will be coordinated. Spearheading these activities will be IAPAC's newly appointed Vice President/Chief Medical Officer, Basil 'Vassily' P. Vareldzis.

Vareldzis earned his Medical Degree in 1986 from the Indiana University School of Medicine. He completed residencies in Family Medicine (1988) and Preventive Medicine (1993) at McGill University and Johns Hopkins University, respectively. In addition, he completed a Master's Degree in Public Health in 1992 at Johns Hopkins University School of Public Health. In addition to his academic credentials, Vareldzis brings vast experience to his new role of coordinating activities to benefit, and generate from, IAPAC's membership of over 12,800 healthcare professionals in 99 countries.

Having worked most recently as a Medical Officer in the World Health Organization (WHO) Department of HIV/AIDS, where he helped to develop antiretroviral treatment guidelines for resource-limited settings, Vareldzis has a background that spans a variety of positions in direct care and international public health. He has worked as an HIV-treating physician since 1986. He founded the American Public Health Association (APHA) HIV/AIDS section; held academic appointments at Johns Hopkins University, Georgetown University, and Virginia Tech; and acted as a Senior Technical Advisor to the US Agency for International Development (USAID).



Basil P. Vareldzis

Vareldzis states that he is eager to begin work at IAPAC. He believes the association is addressing the AIDS pandemic via methods he regards as indispensable to stemming the devastation of a disease that currently infects 42 million people and could easily become, if it is not already, the most destructive disease in world history.

"IAPAC has a critical role to play in empowering the global healthcare community to treat HIV," Vareldzis said. Having trained 12,000-plus African healthcare professionals in southern Africa as exclusive training provider in the Diflucan Partnership Program (DPP), and initiated a much-needed training and certification program in the Global AIDS Learning & Evaluation Network (GALEN), he continued, "the association is poised to make increasing contributions; I am enthusiastic about further mobilizing the IAPAC membership in that direction."

Geneva was chosen for Vareldzis's base of operations within IAPAC because the Swiss city is home to many of the international organizations with which IAPAC partners in the global fight against HIV/AIDS. Along with the WHO, Geneva serves as headquarters for the Joint United Nations Program on

HIV/AIDS (UNAIDS); the Global Fund to Fight AIDS, Tuberculosis and Malaria; and the International Treatment Access Coalition (ITAC), of which IAPAC is a founding partner.

"We have had, since 1996, a very effective means through antiretroviral therapy of treating HIV and prolonging and improving the lives of HIV-infected patients," Vareldzis stated. "While almost every international health organization agrees that access to this treatment must be vastly expanded, only about 800,000 of the world's 42 million people with HIV are treated with antiretroviral therapy. In addition to making antiretroviral drugs more affordable in the developing countries that have been hardest hit, we must make sure that healthcare professionals are armed with the knowledge they need to administer them properly—to manage their side effects and complications, to ensure patients adhere to prescribed regimens, to guard against drug resistance. This is where IAPAC shoulders its share of the burden."

IAPAC President/CEO José M. Zuniga said the IAPAC Technical Annex in Geneva will complement the work of IAPAC's African Regional Office (IAPAC-AFRO) in Johannesburg as well as the association's Headquarters in Chicago.

"Under the leadership of its Executive Director, Mulamba Diese, IAPAC-AFRO is training thousands of healthcare professionals how best to treat the lethal opportunistic infections associated with HIV, and continues to build capacity through which we may responsibly expand access to antiretroviral therapy," Zuniga said. "With Basil Vareldzis joining us in Geneva, IAPAC can build on this experience as we use GALEN and other educational and technical assistance vehicles to bring medical knowledge, including about the use of antiretroviral therapy, to HIV-treaters in resource-limited settings on the African continent and, indeed, around the world." ■



P E R S P E C T I V E

Assessment of changes in adherence and quality of life after the simplification of antiretroviral treatment

Carmina R. Fumaz and
Bonaventura Clotet

Despite the undoubted benefits of antiretrovirals,^{1,2,3} control of the human immunodeficiency virus is only maintained effectively if treatment is taken without interruptions, respecting not only the number of doses and pills, but also the dosage conditions. Proper adherence is a key element in optimizing the efficacy of the drugs prescribed.⁴ The consequences of inadequate adherence are widely known: emergence of mutations in the viral genome that confer resistance to specific antiretrovirals, possibility of cross resistance among drugs of the same family that may limit the future therapeutic alternatives, transmission of resistant HIV strains, and increased economic burden on society.⁵

A treatment regimen's complexity has been shown to be strongly related to adherence.^{6,7,8} Experts on the topic of adherence have warned of the need to design simpler antiretroviral regimens without losing the therapeutic potency.⁹ Drugs may also be extremely toxic,^{10,11} causing adverse events that may diminish considerably patients' quality of life. A relationship between adherence and quality of life has been suggested, although a causality is not clear.¹²

New therapeutic strategies: Simplification of treatment

In recent years one of the main efforts of the scientific community has been focused on developing therapeutic strategies based on simplified antiretroviral regimens. Simplification strategies are defined as the switch from a known, efficacious, yet complex therapy to a simpler but equally potent one. Thus, patients' quality of life and adherence to treatment may benefit from this switch.¹³ The most common

simplification strategies used to date have been based on switching older protease inhibitors (PIs) to newer formulations that require fewer pills or doses, or to PI-sparing regimens (using efavirenz, nevirapine, and abacavir).¹⁴ Recently, several studies have been designed to assess the efficacy of treatments administered once a day.¹⁵

Impact of simplified treatments on patients' adherence and quality of life

To date, studies assessing the impact of switching PI-containing regimens to those containing other drugs such as abacavir or nonnucleoside reverse transcriptase inhibitors (NNRTIs) on adherence and quality of life are still scarce. Clumeck et al, in a study based on replacing a PI with abacavir, revealed that, while adherence in the abacavir group improved at week 48 of follow-up, it diminished with respect to baseline in the PI group at week 48.¹⁶ Barreiro et al evaluated adherence and quality of life in patients that replaced the PI with nevirapine and found that therapeutic failure attributable to lack of adherence was 90 percent in the PI group while only 22 percent of patients failed due to inadequate adherence in the nevirapine group.¹⁷ Also, quality of life increased significantly in the patients taking NNRTIs. However, we have observed the contrary assessing adherence and quality of life in a group of HIV-infected patients for whom initial treatment with PI-containing regimens failed. Patients were randomized to switch their therapeutic regimen to either two nucleoside reverse transcriptase inhibitors (NRTIs) plus efavirenz or two NRTIs plus one or more new PI. No significant differences in adherence levels existed when both groups were compared. However, an important improvement in quality of life was noted in the efavirenz group.¹⁸ When

patients were asked about this improvement, 44 percent of them attributed it to the simplification of therapy. The lack of statistical differences in adherence may be attributed to the fact that all patients received educational counseling about adherence in each visit during the follow-up.

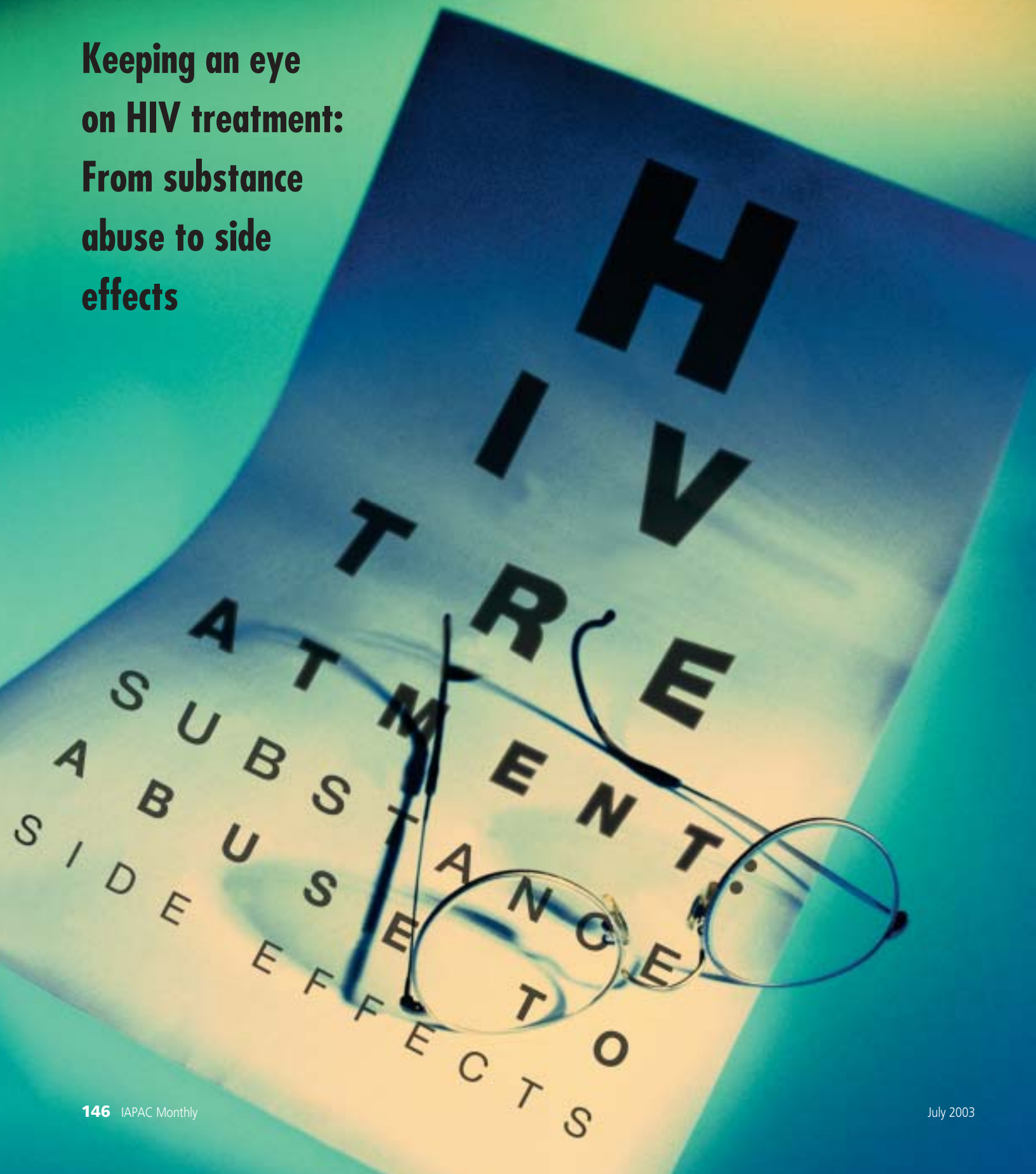
Individuals chronically nonadherent may benefit from simpler regimens. Accordingly, Knobel et al developed a prospective study in which patients with virologic failure (HIV RNA >5,000 copies/mL), a two NRTI + PI-containing therapy and severe nonadherence (less than 50 percent of consumption of prescribed doses or withdrawal) were switched to Combivir + abacavir and later on to Trizivir (when approved). At week 24 of follow-up, 50 percent of patients reported a level of adherence higher than 90 percent and 44 percent of patients had HIV RNA levels <500 copies/mL.¹⁹

Still lacking are data on patients receiving treatment once a day (QD). This therapeutic strategy is novel and its long-term clinical and virological efficacy has yet to be fully determined. Smith presented a study at the XIV International AIDS Conference showing results from a survey of 536 HIV-positive patients.²⁰ Eighty percent of subjects affirmed that it was easier to remember to take medication in a QD regimen while 65 percent of patients thought that a twice-daily (BID) regimen provided greater facility in remembering to take medication.

In a study developed by our team, switching to a QD regimen was related to the improvement of several health-related dimensions in the MOS-HIV questionnaire: mental health, energy, and general quality of life.²¹ Patients also indicated a greater degree of facility in taking medication, preference of the new treatment when compared with the previous, and a higher level of satisfac-

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**Keeping an eye
on HIV treatment:
From substance
abuse to side
effects**



Mark Mascolini

Poor William Stewart, Surgeon General of the United States in Lyndon Johnson's White House. Dr. Stewart had the misfortune to make this brave pronouncement in 1967:

The time has come to close the books on infectious diseases. We have basically wiped out infection in the United States.

Other equally luminous visionaries made similar predictions at the time, but Stewart's words were the ones remembered by Charles Hicks (Duke University, Durham, North Carolina) when he opened the IAPAC Sessions 2003, a two-day by-invitation meeting of veteran HIV clinicians—on both sides of the speaker's lectern.

Within a year of Stewart's ill-timed avowal, researchers now calculate,¹ HIV-1 had already crossed the US border and—almost immediately—began its exponential spread. Even when clinicians in Los Angeles and elsewhere started noticing symptoms of this new infection, its gravity escaped many. Hicks noted, for example, that the 1981 *MMWR* issue announcing "Kaposi's sarcoma and *Pneumocystis* pneumonia among homosexual men" ran on an inside page.² The lead article explored the menace of "Dengue type 4 infection in US travelers to the Caribbean."

These days, on the contrary, a worried citizenry can track new infectious diseases on the first page of the local newspaper—even those that pose a slimmer threat than the plucky retrovirus. IAPAC Sessions delegates, most of whom have treated HIV-infected people since pre-zidovudine days, well understand the vicissitudes of public attention. They know that sometimes too much attention can distract as much as too little attention can dismay. All recognized the legendary *Newsweek* cover that Hicks resurrected via PowerPoint. As the protease inhibitor (PI) era dawned, *Newsweek* asked if we could anticipate "The End of AIDS?" Those three-drug combos certainly changed the face of the epidemic, but at a price. The *Newsweek*

cover suggests part of that price—side effects, intolerance, poor adherence—in the appealing regimen depicted. Hicks observed that it included two big favorites, full-dose ritonavir and chewable didanosine (ddI).

Happily, highly active antiretroviral therapy (HAART) has changed for the better. Hicks traced the accelerated rate of approval—one drug in the 1980s, five from 1991 to 1995, nine from 1996 to 2000, three already since 2001, and more nearing the pipeline's end. As a result, intent-to-treat analyses of some recent trials show 48-week sub-50-copy rates exceeding 80 percent.

Of course many people with HIV, even in wealthy countries, don't share in that success story. As one delegate noted, while drawing knowing nods from colleagues, "I have patients whose list of drugs taken is the list of drugs available." But even people starting antiretroviral therapy now, and starting before getting an AIDS-defining disease, face more than one obstacle with these multidrug regimens. IAPAC Sessions planners framed the meeting around several of these obstacles—coexisting disease and substance abuse, risks and benefits of simpler regimens, poor adherence, variable pharmacokinetics, resistance, and metabolic side effects.

Hepatitis, mental illness, and substance abuse: Managing the triple-diagnosed HIV patient

Patricia C. Kloser
New Jersey Medical School, Newark

While antiretroviral therapy continues to evolve, some things don't change. Working in Newark with poor and often indigent people, Patricia Kloser has seen more than one "triple-diagnosed" person—with hepatitis, mental illness, and substance abuse on top of HIV. So she often diagnoses HIV infection the same way clinicians did in the early 1980s—by diagnosing an AIDS-defining disease first.

Just in the past week, she noted, one man sought care with *Pneumocystis carinii* pneumonia (PCP) and a CD4 count of 50 cells/mm³, and another came in with central nervous system (CNS) lymphoma.

That happens everywhere, not just in Newark. But it happens more in poor inner cities rife with unemployment, homelessness, crime, substance abuse, high resident turnover, and lack of social contact. All of those problems may contribute to a disorder that routinely complicates management of HIV infection—mental illness.

Keys to confronting mental illness

The major mental illness Kloser faces in her HIV clinic is depression, which has its seeds not only in HIV infection, but also possibly in cocaine use or alcoholism. Depression remains highly underdiagnosed in people with and without HIV. Kloser proposed the symptom clues appearing in Table 1, adding that a blinkered focus on CD4 counts and viral loads can make clinicians overlook depression.

A good opening question when evaluating a person for depression, Kloser suggested, is "How have you felt over the last days and weeks?" If the patient doesn't understand, be more specific: "Do you feel angry? Nervous? Sad? Happy? Has there been anything that made you feel this way?" From there, several other questions can help pin down the details:

- How do you sleep?
- What interests do you have? Have you noticed any change in your interests lately?
- Is there anything you feel guilty about? If so, why? What happened?
- How is your energy?
- How is your concentration?
- What is your appetite like?
- Do you have any thoughts about death or hurting yourself? Do you think you might be better off not being here?

The clinician should also observe whether the patient has psychomotor retardation.

Although depression is the most common mental health problem in people with

Table 1. Depression's three tiers of symptoms

<i>Highly specific</i>	<i>Moderately specific</i>	<i>Less specific</i>
Suicide attempt	Hopelessness, helplessness	Weight loss or gain
Recurrent suicidal ideation	Diminished ability to concentrate	Change in appetite
Feelings of worthlessness	Diminished interest or pleasure	Insomnia or hypersomnia
Excessive guilt	Recurrent thoughts of death	Fatigue
Depressed mood		Loss of energy
Psychomotor retardation		

HIV, patients may also have underlying psychoses such as schizophrenia or bipolar disorder. Kloser mentioned one person with apparent schizophrenia who claimed a voice was telling her not to take her anti-retrovirals. People with bipolar disorder typically fail to keep appointments when at either extreme of their mood swings.

Organic diseases that may cause or contribute to mental problems in HIV-infected people include CNS atrophy, progressive multifocal leukoencephalopathy, toxoplasmosis, cryptococcosis, HIV encephalopathy, and dementia. Kloser stressed the importance of screening for such diseases as well as for metabolic abnormalities.

HIV dementia manifests itself in three spheres. Clues pointing to these problems become easier to spot when a clinician gets to know a patient better:

- *Cognitive*: subtle mental changes, poor concentration, slowed thinking
- *Motor*: abnormal gait, leaning, falling, weakness
- *Behavior*: irritable with labile mood, apathy

HAART itself may rouse neuropsychiatric nettles, including headache, insomnia, neuropathy, nightmares, and—again—depression. In turn, depression and other mental illnesses can promote poor adherence.

Kloser proposed a checklist for managing mental health problems in people with HIV infection:

1. Screen patients for underlying mental illness.
2. Consider risperidone for people with psychosis because it is less likely than other agents to cause extrapyramidal side effects.
3. *Continually* evaluate patients for evidence of depression.
4. Evaluate patients for sleep disorders, and consider trazodone for treatment.

5. Consider selective serotonin reuptake inhibitors for depression because of their low rate of drug-drug interactions.

Kloser emphasized that treatment of mental illness should be planned in consultation with a specialist. But primary clinicians may have to write some prescriptions for psychotropic agents to manage acute problems before a psychiatric consult can be arranged.

Substance abuse and withdrawal

The “big three” abused drugs are cocaine, heroin (often both), and benzodiazepines. A related problem is alcoholism, which Kloser notes especially among the women for whom she cares.

In the United States, cocaine caused 175,000 emergency room visits in 2000, 57 percent of which led to admissions. Kloser spelled out these symptoms of cocaine use:

- Blood pressure, pulse, or respiration may be mildly increased. (You may be treating the person for hypertension.)
- Shortness of breath may not signal pneumonia, but cocaine use before the visit.
- Abnormal sweating is common.

Cocaine has dangerous cardiovascular effects—myocarditis, atherosclerosis, cardiomyopathy, ischemia, and arrhythmia. In Kloser’s cachement, cocaine abuse is most common among black males, but she notes that female abusers have gravitated toward the drug because it doesn’t have to be injected. Most cocaine users also smoke tobacco.

In the Newark area heroin preys on the growing population of immigrants, who often share needles. Heroin has infectious complications—cellulitis, sepsis, endocarditis, and osteomyelitis—and may cause nephropathy, which often comes on suddenly in people with HIV. Dialysis-dependent nephropathy may lead to sepsis resulting from poor shunt care and even

Table 2. Hepatotoxic non-HIV agents commonly taken by HIV-infected people

- Isoniazid
- Rifampin
- Oral contraceptives
- Azole antifungals
- Acetaminophen
- Macrolide antibiotics
- Anabolic steroids
- Testosterone
- Amitriptyline
- Ibuprofen
- Sulfonamides
- Phenytoin

illicit use of shunts. Hypertension frequently accompanies nephropathy.

Severe depression, delusions, and paranoia may signal heroin withdrawal. Although propranolol and the antidepressants desipramine and bupropion may help in the acute phases of withdrawal, there is no good treatment. Buprenorphine or methadone may also ease heroin withdrawal, and clonidine may diminish the severity of symptoms. Rapid and ultrarapid detoxification programs use a variety of medications and naloxone-induced withdrawal under anesthesia or heavy sedation. Inpatient detox programs have proved more successful than outpatient programs.

The many threats of hepatitis

No one argues that the key to survival with HIV infection is HAART, Kloser noted. But advanced liver disease makes HAART intolerable. Especially in the form of hepatitis virus infection, liver disease has become a subepidemic among people with HIV infection, and especially among substance abusers who share needles. Kloser considered four types of hepatitis:

- Toxic and drug-induced hepatitis
- Alcoholic hepatitis
- Acute viral hepatitis
- Chronic viral hepatitis

Toxic, drug-induced hepatitis is often idiosyncratic and unpredictable but not dose dependent. Often caused by drug metabolites, toxic hepatitis manifests itself differently from person to person and can be confused with infectious hepatitis. Kloser ticked off a laundry list of hepatotoxic

agents taken by HIV-infected people (Table 2^{3,4}). One could add the antiretrovirals zidovudine (AZT), ddI (especially when combined with stavudine [d4T]), nevirapine, indinavir, and atazanavir. Because isoniazid and rifampin assault the liver, Kloser added, liver function test variables are almost always elevated in people taking those agents for tuberculosis. But the clinical side effects of those drugs vary.

Alcoholic hepatitis usually leads to irreversible and progressive chronic liver injury. Besides causing hepatitis, alcohol can promote fatty liver (hepatic steatosis) and cirrhosis. The three conditions usually appear together and can be compounded by other liver insults. The quantity of alcohol and duration of use needed to cause cirrhosis are uncertain, but the type of drink is probably less important than quantity and duration. Poor nutrition, female gender, and diminished rates of alcohol metabolism may predispose a person to cirrhosis.

Kloser noted that 15 to 20 percent of people in general primary care practice report alcohol-related health problems. The CAGE questions, she said, can help identify alcoholics:

C: Can you cut down on your drinking?

A: Are you annoyed when asked to stop drinking?

G: Do you feel guilty about your drinking?

E: Do you need an eye-opener drink when you get up in the morning?

Care for an alcoholic patient must be supportive and nonjudgmental, yet assertive. Kloser finds that self-help groups alone are not enough to help people stop drinking. Clinicians caring for an alcoholic patient should be prepared to treat withdrawal symptoms (delirium, tremors, seizures) and to order inpatient treatment for severe depression, suicidal ideation, or psychotic symptoms. Benzodiazepines, carbamazepine, and valproate can promote seizure-free withdrawal.

Hepatitis A affects 40 to 70 percent of US residents with HIV infection by age 30. Markers of hepatitis B virus turn up in 60 to 80 percent of injecting drug users. Kloser stressed the urgency of preventing both by vaccination. Between 150,000 and 300,000 US residents with HIV infection also have hepatitis C virus (HCV). HCV may be a marker for:

- Addiction
- Poor access to care
- Later institution of HAART

More than three alcoholic drinks daily speeds progression of liver disease. Yet in one Veterans Administration study, 30 percent of people with HCV infection also drank alcohol.⁵ Every effort should be made to help HCV-infected drinkers stop.

Recent outbreaks of hepatitis D infection have been noted among drug abusers, with a fatality rate of 5 percent. When people infected with hepatitis B also become infected with hepatitis D, the fatality rate climbs to 20 percent. Hepatitis E is less common in the United States but is a concern in developing countries.

Liver transplants have proved successful in carefully selected people with HIV. Selection criteria include stable antiretroviral therapy, a CD4 count above 200 cells/mm³, and a low or undetectable viral load. “Ten years ago,” Kloser confessed, “I wouldn’t have dreamed this would be possible.”

Antiretrovirals for “triple-diagnosed” patients

What antiretroviral regimens does Kloser prefer for people burdened by mental illness, substance abuse, and/or hepatitis: a simpler, more tolerable nonnucleoside (NNRTI) combination, or a PI regimen with a higher barrier to resistance? She often opts for a simpler regimen, but first, Kloser added, “you have to teach that person how to be a patient.” Because this could well be a patient’s first contact with healthcare, she may try to establish adherence by prescribing a vitamin or PCP prophylaxis and monitoring carefully. Ironically, she noted, it may be easier to explain the importance of adherence to a drug user who understands the grave consequences of missing a day’s dose.

If antiretroviral therapy must begin before adherence can be established, Kloser leans toward Trizivir, the three-in-one pill combining AZT, lamivudine (3TC), and abacavir. Besides being the simplest of regimens, its failure—which usually starts with resistance to 3TC—leaves an array of backup options.

Trizivir suffered a recent setback, though, in a randomized comparison with efavirenz regimens. And preliminary analysis of that study left much grist to mill during Charles Steinberg’s presentation on simplified antiretroviral regimens.

21st century regimens: Is simpler better?

*Charles L. Steinberg
Boulder Community Hospital
Boulder, Colorado*

Is simpler better? Charles Steinberg had a simple answer: Yes.

At least we humans intuitively sense that simpler almost always works better in the long run. Just look at antiretroviral therapy. The granddaddy of all HAARTs—AZT, 3TC, and indinavir—raised eyebrows and dropped jaws in the Merck 035 study, convincing all that these new triple therapies handily surpassed single and dual nucleosides in potency. But the 035 regimen wasn’t exactly easy to take. The ideal patient, Steinberg reminded colleagues, took the combo in nine discrete steps:

1. Eat breakfast + AZT + 3TC
2. Take indinavir + water
3. Drink water
4. Eat lunch + AZT
5. Take indinavir + water
6. Drink water
7. Eat dinner + AZT + 3TC
8. Take indinavir + water
9. Drink water before bed

Who could have guessed that less than a decade later easy once- and twice-daily regimens—with no dietary or aqueous codicils—would abound? It’s true that planning therapy remains tough for the prescriber, but fewer pills, scarcer side effects, and convenient coformulations can make treatment much simpler for the patient (Table 3).

Beneath this rosy veneer—at least for the antiretroviral initiate—lurk many of the same questions faced when HAART left the controlled trial and first hit the clinic:

- Safety?
- Efficacy?
- Durability?
- Resistance?
- Fewer simple options later?

Those considerations made Steinberg modify his “yes” to a “yes, but.”

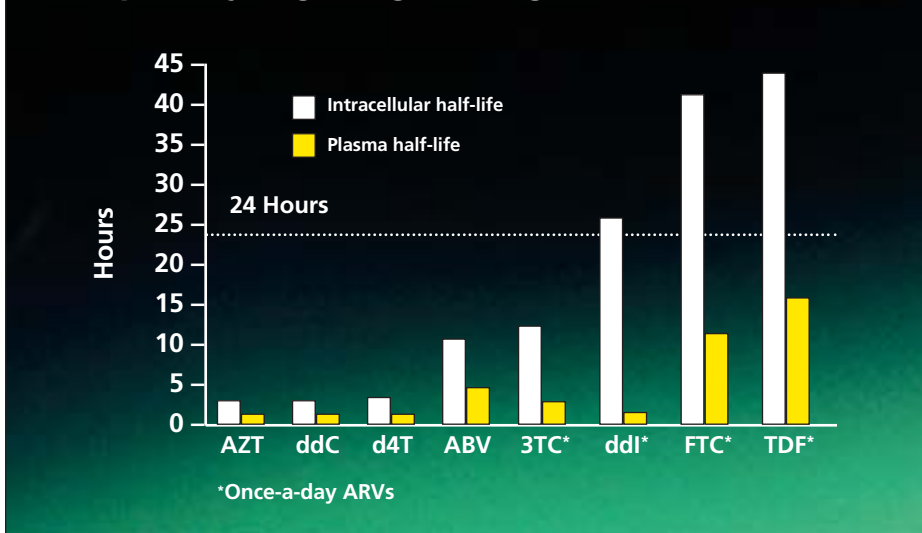
Safety

While simpler may always be easier, it’s not always safer. Steinberg referred

Table 3. Antiretroviral therapy today: Complex yet simple

Complex for the clinician	Simple (sometimes) for the patient
<ul style="list-style-type: none"> • Latest studies • Drug-drug interactions • Side effects, metabolic changes • Resistance and cross-resistance • Adherence • First, second, third, and salvage regimens • Monitoring, resistance testing • Treatment failure, switching • Structured treatment interruptions • Cost and availability 	<ul style="list-style-type: none"> • Fewer pills • Once- or twice-daily dosing • Coformulations with fewer copays • Minimal food requirements • Minimal side effects • Minimal drug-drug interactions • Closely linked to daily routine

Figure 1. Intracellular half-lives of ddi, FTC, and tenofovir are probably long enough to “forgive” a missed dose.



colleagues to results of the 2NN study, which compared once-daily nevirapine, twice-daily nevirapine, once-daily efavirenz, and efavirenz/nevirapine.⁶ After 48 weeks of treatment, liver function tests were elevated in 13.2 percent taking once-daily nevirapine versus 7.8 percent taking the standard twice-a-day dose. The higher rate with once-daily dosing could reflect the higher peak concentrations when a person swallows 400 mg of nevirapine all at once.

But once-a-day strategies with twice-a-day drugs don't always turn out bad. Take, for example, once-daily extended-release d4T (d4T-XR) compared with the twice-daily immediate-release formulation. The peak concentration with twice-daily dosing (694 ng/mL) more than doubles that with the XR version (339 ng/mL). In the clinic that difference has translated into lower reported rates of peripheral neuropathy, hyperlactatemia, pancreatitis, and lipodystrophy.

Most antiretrovirals favored in simpler

regimens, however, have familiar and—for some—inescapable side effects:

- Trizivir: abacavir hypersensitivity reaction
- Efavirenz: CNS toxicity
- Nevirapine: hepatotoxicity, Stevens-Johnson syndrome
- Atazanavir: hyperbilirubinemia
- Enteric-coated ddi (ddI-EC): pancreatitis

Forgiveness

A nagging concern with once-a-day dosing is its possibly unforgiving nature. *Forgiveness* has become the term favored to explain a drug's ability to hang around long enough, at levels *high* enough, to prevent emergence of resistant virus even if a dose is missed. When people miss a once-daily dose, they could wind up going 48 hours without sending any drug cellward.

But Steinberg stressed that the half-lives of many once-daily drugs are probably long enough to “forgive” a missed dose: Efavirenz, nevirapine, tenofovir, and ddi-EC

Table 4. Reasons for missing doses addressed by simpler regimens

Reason for missing dose	Respondents (%)	Addressed by simpler regimen?
Too busy/simply forgot	52	Yes
Away from home	46	Yes
Change in daily routine	45	Yes
Felt depressed/overwhelmed	27	No
Took drug holiday	20	No
Ran out of medication	20	No
Too many pills	19	Yes
Worried about becoming “immune”	19	No
Felt drug was too toxic	18	No
Wanted to avoid side effects	17	No
Didn't want others to notice	17	Yes
Reminder of HIV infection	16	Yes
Confused about dosage directions	14	Yes
Didn't think it was improving health	13	No
To make it last longer	10	No
Told the medication is no good	9	No

Adapted from reference 8.

fall into that group. Other drugs that already—or may later—do once-daily duty have shorter half-lives: 3TC and abacavir, for example. With nucleosides and the first nucleotide, Steinberg reminded delegates, what matters is not the plasma half-life but the intracellular half-life. By that measure ddi-EC, tenofovir, and the investigational nucleoside emtricitabine (FTC) all look like friendly forgivers (Figure 1). Again, 3TC and abacavir do not. A US Food and Drug Administration (FDA) sanctioned once-daily boosted PI, amprenavir/ritonavir (1,200/200 mg) also sustains high levels through 48 hours.

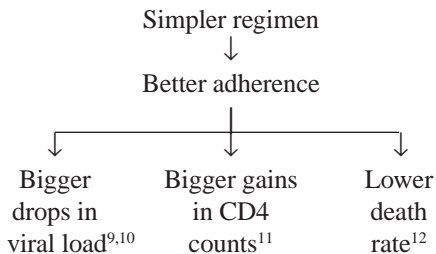
Even with less forgiving regimens, Steinberg said, greater simplicity may improve adherence. Although some early studies on antiretroviral adherence suggested little difference between once-daily and twice-daily regimens, a smattering of recent work gives the nod to once-a-day payloads. A European survey of 504 people taking once-a-day, twice-a-day, three-times-a-day, or more than three times-a-day regimens found that 40 percent, 63 percent, 66 percent, and 71 percent respectively missed doses.⁷

This five-country study also found that the number of pills in a regimen determines

whether people will take them all in one sitting: Whereas 92 percent said they would take three pills once a day and 84 percent said they would take four pills, only 59 percent would agree to swallow six pills all at once and 38 percent eight pills. An unpublished 265-person US survey confirmed those trends: 73 percent liked the idea of downing four pills once a day. In comparison, only 18 percent favored an easy-sounding one pill in the morning and two at night.

Cutting down pill counts or simplifying schedules would address several problems that people cite when asked why they miss doses. Steinberg showed the results of one survey of 133 people who gave 16 reasons for missing a dose.⁸ Taking fewer pills less often might solve seven of these problems, including the three most frequent (Table 4).

Steinberg's simplification argument can be boiled down to a simple flow chart:



How simple to simplify?

How simple is it to build a simple regimen? Pretty simple, nowadays, even when thinking about second- or third-line regimens.

The nucleoside/nucleotide wedge of a once-daily pie can now draw on four drugs:

- Tenofovir
- 3TC
- ddI-EC
- d4T-XR

FTC may soon be another nucleoside ingredient. The NNRTI-PI piece already includes:

- Efavirenz
- Amprenavir/ritonavir
- Saquinavir/ritonavir
- Atazanavir

Other agents being studied in once-daily regimens are nevirapine, lopinavir/ritonavir, abacavir, and the second-generation fusion inhibitor T-1249.

Long-range planning with a treatment-

naive person could even yield a scheme for a not-too-daunting three-regimen sequence, Steinberg suggested, referring to a presentation by Graeme Moyle (Chelsea and Westminster Hospital, London) at the 2002 Glasgow meeting:

1. ddI-EC, 3TC, efavirenz: three pills once daily on empty stomach
2. d4T-XR, tenofovir, atazanavir: four pills once daily with food
3. Abacavir, tenofovir, lopinavir/ritonavir: five pills with breakfast, four with dinner

First-line Trizivir: too early to “junk”?

But there's a problem with this scenario, one delegate noticed. While all these regimens and many other possibilities look good on paper, few have ventured through the clinical trial gauntlet. This is no quibble, as an interim analysis of ACTG 5095 shows. The trial randomized treatment-naive people to one of three arms: Trizivir, Trizivir plus efavirenz, or Combivir (AZT/3TC) plus efavirenz. The study's independent review board stopped enrollment into the Trizivir-only arm when a higher proportion of people in that group (21 percent) than in the combined efavirenz arms (10 percent) reached a protocol-defined virologic failure after an average 32 weeks.¹³ Time to virologic failure proved significantly shorter in the Trizivir arm ($P < 0.001$). And among 33 percent of people who reached study week 48, 74 percent taking Trizivir alone versus 89 percent in the efavirenz arms had a viral load below 200 copies/mL. Trizivir failed in equivalent proportions with baseline loads above and below 100,000 copies/mL.

Is simpler really worse when it comes to this one-pill-twice-daily regimen? The British HIV Association thinks so, suggesting in its 2003 draft guidelines that clinicians avoid first-line Trizivir.¹⁴ But several clinicians at the IAPAC Sessions think it's too early to tell. Steinberg observed that blinding the ACTG 5095 trial stripped Trizivir of its simplicity because people in the Trizivir-only arm had to take five dummy pills along with their two Trizivir tabs.

One delegate argued that clinicians shouldn't “junk the whole concept” of first-line Trizivir until the ACTG presents a fuller 5095 analysis. Will we learn something by finding out who endured the Trizivir failures? Do they represent some subgroup in whom first-line Trizivir may

indeed pose a higher risk of failure? IAPAC Sessions Co-Chair Renslow Sherer (University of Chicago Hospitals) added that the preliminary response rate in the solo Trizivir arm wasn't that awful—74 percent under 200 copies at 48 weeks in an intent-to-treat analysis. For now, Sherer said, he will continue to prescribe up-front Trizivir for selected individuals, for example, someone who asks for a simple regimen, has a viral load under 100,000 copies/mL, and has some reason not to start with an NNRTI.

To balance his summary of why simpler drug medleys may not be better, Steinberg summed up several reasons why they may:

- They work.
- Patients like them.
- They improve adherence.
- They have a lower “burden” (including the psychological burden of chronic medication).
- They're less toxic (by chance).
- They have a better chance of reaching the still-untreated 95 percent.

Adherence: New lessons learned, old caveats confirmed

Judith E. Feinberg
University of Cincinnati

Successful adherence, some say, means taking at least 80 percent of doses. But Judith Feinberg observed that HIV medicine inherited this benchmark from the antihypertensive literature and that “it may have nothing to do with anti-infective prescribing.” To complicate things, this notion of successful adherence paid no special attention to intervals between doses or dietary restrictions. “Eighty percent adherence,” Feinberg said, “is not going to get you below 50 copies.”

So what is successful adherence for HAART? Two studies suggest that it lies somewhere above 90 percent of all doses, but accurate estimates probably vary with the regimen. The classic study of anti-retroviral adherence by David Paterson and colleagues found that 80 percent of people who were more than 95 percent adherent to a PI regimen had a viral load under 400 copies/mL after three months of therapy.¹⁵ Only about 60 percent of people who had a 90 to 95 percent adherence score reached that level of suppression.

Table 5. Factors that can and cannot predict adherence

Positive predictors	Negative predictors	Not predictive
<ul style="list-style-type: none"> • Patient belief in HAART • Physician experience • Social support • Adherence to office visits 	<ul style="list-style-type: none"> • Active drug use • Alcohol abuse (>14 drinks/week) • Active psychiatric disease • Cumulative impact of HIV • Socioeconomic status 	<ul style="list-style-type: none"> • Race • Gender • Disease stage • History of substance abuse

Sources: Ostrow D, Fox K, Kleeberger C, et al. Psychosocial correlates of incomplete adherence to HIV antiretroviral therapy: mental health matters. 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001. Chicago. Abstract 484; Gebo KA, Keruly JC, Moore RD. Is illicit drug use a risk factor for non-adherence to antiretroviral therapy? 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001. Chicago. Abstract 477.

Table 6. Three sets of factors that may affect adherence

Disease/treatment factors	Interpersonal factors	Personal/patient factors
<ul style="list-style-type: none"> • Medication itself (number, size, and taste of pills) • Regimen requirements (practical and cognitive demands) • Side effects (frequency, severity, perceived causes, short- versus long-term, fear of side effects) • Drug interactions • Comorbidities • Treatment history • Physical condition; disease state 	<ul style="list-style-type: none"> • Doctor-patient relationship (communication, trust, support) • Social network (having others to care for, having others available) • Living conditions (facilitating versus impeding) • HIV disclosure concerns 	<ul style="list-style-type: none"> • Knowledge and understanding of disease and therapy • Attitudes and cultural beliefs about taking medicines • Expectations and motivations • Personality • Stress • Daily lifestyle; human error (forgetting) • Substance use/abuse • Psychiatric conditions; cognitive function • Economic status

Source: Chesney MA. Factors affecting adherence to antiretroviral therapy. *Clin Infect Dis* 2000;30(suppl 2):S171-S-176.

Some have observed that Paterson’s study, conducted from 1997 to 1999, evaluated unboosted PIs and not the more user-friendly—and often more forgiving—boosted PI, nonnucleoside, and Trizivir regimens of today.

A later study that compared Combivir/abacavir with Combivir/indinavir found that almost everyone with 90 to 95 percent adherence to the triple-nuke regimen had a 48-week viral load below 400 copies/mL.¹⁶ But only about 65 percent of people with that level of adherence to Combivir/indinavir notched a sub-400 viral load. When adherence exceeded 95 percent, the two groups achieved equivalent levels of viral suppression. A second recent study also found that only near-perfect adherence—better than 95 percent—correlates with durable suppression of viremia below 50 copies/mL.¹⁷ Worse adherence raised the risk of virologic breakthrough.

Why people miss their doses

An ACTG survey confirmed what seasoned HIV clinicians know about why people skip antiretroviral doses:

- They forget.
- They fall asleep.

- They’re too busy.
- They’re depressed.
- They’re away from home.
- Their medicines make them sick.

A survey of 196 women charted four key reasons for poor adherence: 57 percent forgot, 39 percent complained of side effects, 22 percent “felt well,” and 20 percent suspected their antiretrovirals weren’t working.¹⁸ Although the just-noted study of Combivir/abacavir versus Combivir/indinavir found better adherence to the all-nucleoside regimen,¹⁶ the reasons for poor adherence were similar with both regimens: forgetting, being out in public, and side effects.

No one can predict with certainty who will adhere well to antiretroviral combos and who will not. During a discussion, Richard Elion (George Washington University, Washington, DC) noted that four of eight gay white men enrolled in a treatment support group attended sessions for a full year before confessing their slipshod adherence. On the other hand Feinberg cited the case of a homeless woman who wanted to enroll in an antiretroviral trial. When Feinberg asked how she’d manage

to take her drugs on time, she answered, “I could if I had a watch.” Feinberg bought her a watch and she had the best drug levels in the group. Still, Feinberg proposed that certain variables often work as positive or negative predictors of adherence, while others are not predictive (Table 5).

Yet, after practicing HIV medicine for 20 years, Feinberg believes the central determinant of adherence is some innate, immeasurable factor that she calls “personality.” Some people can take a handful of pills and swallow them in several gulps, right on schedule; some can’t. Feinberg feels she may be able to coax this trait forward or “tune it,” but she doesn’t think she or any clinician can make a bad adherer a good one.

Sometimes bad adherence, Feinberg suspects, reflects ineradicable guilt “about whatever they did to get HIV.” They cope with that guilt by seeking punishment—and a certain way to do that is to shun their medications. She offered an anecdote of a 27-year-old man who rarely took his antiretrovirals and died with a highly treatable 3TC-resistant virus. At the other end of the spectrum sit people who are perfectly content with their every-eight-hour indinavir and wouldn’t *dream* of tinkering that into a twice-daily ritonavir boost. Despite such intangibles, Feinberg urged colleagues to flip through their mental checklist of factors that may affect adherence whenever planning therapy or addressing potential poor adherence (Table 6).

Although the latest antiretroviral regimens are simplicity incarnate compared with the first HAART combos—not to mention the original five-times-daily AZT—the prospect of taking drugs regularly for the rest of one’s life can make anyone a faulty adherer. During his adherence talk (see next section), Elion recalled his humbling brush with postexposure prophylaxis. Even when faced with this short and circumscribed course of therapy, he found perioral paresthesia and headaches powerful motivators to stop.

Beyond the burden of side effects, Feinberg noted, a certain percentage of people invariably misunderstands dosing directions. And that percentage grows as treatment continues. In an observational cohort of 289 women, researchers found that 80 percent started off understanding food restrictions, 75 percent understood dosing frequency, and only 63 percent understood both.¹⁹ The proportion of

women who understood dosing frequency fell with time. Women who correctly understood dosing and were taking once- or twice-daily regimens with no food restrictions had a 60 percent lower chance of skipping doses in the preceding three days than did women taking more complex regimens.

How to encourage adherence

Feinberg offered two bedrock dictates of adherence-promoting prescribing:

1. Tailor the regimen to the patient's lifestyle, not the patient's life to the regimen.
2. The best regimen is the one the patient can and will take.

How can a clinician put these dictates into action? *Before* starting antiretroviral therapy, Feinberg suggests four steps:

- *Assess the patient's readiness for treatment.* Especially in the early days of HAART, Feinberg believes the prescriber was often much readier than the patient. A person about to make a long-term—possibly lifelong—commitment to antiretroviral therapy must first understand the disease and then understand why adherence matters. While explaining what makes HIV tick, the clinician should also assess the patient's attitudes toward antiretroviral therapy.

- *Review treatment options.* Consider how dosing schedules, food and water requirements, and pill count will fit with a person's lifestyle. Feinberg uses a "pill board" display of actual antiretrovirals instead of photographic charts. The flattened two dimensions of charts, she believes, can be deceiving. Some people, the lucky ones, have no problem with the number or size of pills; others will resort to taking one amprenavir capsule every 15 minutes until the complete dose is downed.

- *Educate the patient.* Before starting therapy people should understand the potential side effects of their new regimen and how to manage them. Feinberg finds out which possible side effect a person fears most, then avoids drugs that may cause it. She favors "pre-emptive strikes" for preventable side effects, like nausea and diarrhea, during the first weeks of therapy.

- *Set realistic expectations for optimal adherence.* With the patient, decide what viral load and CD4 count to aim for. If possible, avoid concomitant medications that may complicate therapy or raise the risk of side effects.

Adherence tools—pill boxes, medication

charts, calendar stickers, timers—can help some people. Of these, Feinberg finds that pill boxes work best for her patients. Finally, clinicians must remember that adherence counseling only *begins* before the first dose. It must continue throughout therapy, as part of regular monitoring.

Proactive prevention of poor adherence

When Feinberg feels adherence may be difficult for someone, she addresses potential problems up front. Besides recognizing and addressing mental illness and drug use (see the presentation by Patricia Kloser), Feinberg tries to help people overcome fundamental obstacles like transportation, housing, and psychosocial support. IAPAC Sessions Co-Chair Renslow Sherer believes his team increases retention in the clinic about 20 percent by providing transportation. If that's not possible, he suggests trying the tactic Paul Farmer (Harvard University) uses in Haiti—recruiting a family member or neighbor to visit people taking antiretrovirals and encourage full adherence.

Like Farmer, Feinberg enlists family or friends in the effort. She asks people starting antiretrovirals to bring a friend or family member to pretreatment discussions about therapy. Under less stress than the patient, that person often remembers more when treatment begins. If some type of time-limited directly observed therapy (DOT) is feasible, Feinberg thinks it can get some people off on the right foot.

Each patient's regimen should be selected for optimal convenience, simplicity, tolerability, and potency. For people starting therapy, Feinberg sticks to once- or twice-daily combinations. She believes, though, that an advantage for once-daily dosing over twice-daily dosing remains uncertain. Data comparing the efficacy of once- versus twice-daily regimens are sparse, while limited data link once-a-day regimens with better adherence. The "forgiveness" of once-daily combinations is not well understood. (See the presentation by Charles Steinberg for more on adherence and forgiveness with once-daily therapy.) Pharmacokinetic considerations such as interpatient variability, intracellular concentrations, and drug-drug interactions may have a greater impact on once-a-day combos.

What to do about poor adherence

Feinberg suggests a two-part approach when adherence goes awry despite the best planning:

1. Determine the barriers to adherence, including psychosocial problems, healthcare system impediments, and knowledge gaps.
2. Don't be judgmental. Anticipate that people will misunderstand instructions. To avoid or correct misunderstanding, ask patients to repeat your instructions in their own words.

When resources allow, other stratagems can help resolve adherence problems:

- Increase the intensity of clinical follow-up.
- Shorten the follow-up interval.
- Offer flexible clinic hours.
- Employ bilingual staff members.
- Recruit additional healthcare team members, such as mental health specialists and chemical dependence counselors.
- Use an HIV specialty pharmacy.
- Involve family, friends, and community.
- Consider DOT or modified DOT programs.

Feinberg summed up her insights on adherence with this advice:

- **Beware of stereotypes and prejudice,** but know the positive and negative predictors of adherence (Table 5).
- **Anticipate common causes of poor adherence not related to the medication.** These causes include mental illness, drug use, homelessness, life instability, and poor clinic attendance.
- **Watch out for pill fatigue.** Even excellent adherence may wane over time. Always keep pill burden and dosing frequency in mind.
- **Get it right the first time.** Establish readiness before starting antiretrovirals.

For further adherence advice, Feinberg listed some online sources.²⁰

Adherence: What becomes of the broken-HAARTed?

*Richard A. Elion
George Washington University
Washington, DC*

Adherence matters, said Richard Elion, because today's antiretrovirals can achieve close to 100 percent virologic success in treatment-naive people. Evidence to support this claim comes from a study comparing HIV-infected prisoners

taking directly observed HAART and people taking HAART on their own in ACTG trials.²¹ Everyone in both groups was treatment naive. After 88 weeks all of the prisoners had a viral load below 400 copies/mL, compared with 80 percent in the ACTG trial group.

If the drugs work so well, why are virologic success rates among first-time HAART takers so much lower in clinical practice? Elion gave two reasons: anti-retroviral regimens are demanding, and adherence is poor. Citing Paterson's study linking increasing levels of adherence to higher rates of virologic success,¹⁵ he stressed that "midrange adherence"—taking about 60 to 90 percent of doses on time—is the most fertile breeding ground for drug-resistant virus.

A study comparing two adherence tactics with no intervention supports this contention. Researchers based the comparison on a simulation model using published parameter estimates; they evaluated the model monthly over a one-year simulation in 50,000 people taking antiretrovirals.²² In the no-intervention group adherence averaged 58.9 percent. But in an adherence case management (ACM) group and a modified directly observed therapy (MDOT) group, adherence rates improved to only 67.5 percent and 84.1 percent respectively. Although these higher adherence rates correlated with higher proportions reaching viral loads below 50 copies/mL (16.2 percent for no intervention, 22.4 percent for ACM, and 38.5 percent for MDOT), evolution of drug-resistant mutants proved equivalent across the three groups.

Besides raising the risk of resistance, imperfect adherence poses a public health threat. People who adhere poorly to antiretrovirals tend to adhere poorly to safer-sex guidelines, Elion said. As the prevalence of antiretroviral resistance in the United States grows, so do rates of unsafe sex and sexually transmitted diseases. Several lines of evidence suggest that better adherence may lower the risk of HIV transmission:²³⁻²⁷

- For each one-log increment in viral load, the risk of transmission jumps 2.45 times.
- Sexual transmission of HIV is less likely when an infected partner's viral load lies below 1,500 copies/mL.
- Good adherence lightens viral loads in semen and cervical secretions.

- Lower maternal viral loads trim the risk of perinatal transmission.

Strategies for strengthening adherence

For most people, adherence gets worse as treatment continues. Among the many reasons for this withering resolve as the months roll by, nagging side effects weigh heavily. And the most unsightly yet hardest to hide side effect is lipodystrophy. Elion made the point bluntly: "People don't like to look like they're taking antiretrovirals."

In a study of 74 people infected with HIV for more than five years, 78 percent reported some body shape change.²⁸ While 30 percent had switched their antiretrovirals and 7 percent had stopped them because of lipodystrophy, only 7 percent vowed they would definitely not revamp their regimen because of fat changes. Among people who hadn't switched to different drugs, 57 percent said they were thinking about it, and 46 percent said they would switch if their lipodystrophy worsened. A survey of 75 people attending an HIV clinic found that 20 percent would give up four years of life to avoid lipodystrophy.²⁹ More than 10 percent would give up five or six years.

To counteract waning adherence in people starting HAART, Elion suggested that an updated version of induction-maintenance therapy may work for some. Offer people the option of starting treatment with a PI-based regimen, explaining the advantage of a high barrier to resistance. But hold out the possibility of switching to a simpler yet still suppressive regimen when the viral load becomes undetectable.

A more structured approach to adherence education can pay virologic dividends, according to results of one randomized study involving 116 people starting HAART.³⁰ An "experimental group" received counseling (including information about therapy and the hazards of poor adherence), an adapted medication schedule, and a training session to solve common problems. The control group got standard care. Researchers measured adherence by self-report and plasma drug levels, which mirrored patient reports in 93 percent.

Adherence averaged more than 90 percent throughout the study in the experimental group, while dwindling from 90 percent to about 70 percent in the control group. After 48 weeks 88.9 percent

in the experimental group and 65.8 percent in the control group had a viral load below 400 copies/mL ($P = 0.026$). Among people with better than 95 percent adherence, 85 percent had a viral load below 400 copies/mL.

Another adherence tactic that worked for one group is a pre-HAART practice trial.³¹ The trial may also give clinicians a better fix on who will adhere well once actual therapy begins. The study involved 179 active or current drug users who took a two-week practice run with dummy antiretrovirals. Electronic bottle caps measured adherence during that time. Sixty-five of them later began antiretroviral therapy, and electronic caps again recorded pill taking for two weeks. Adherence during the practice run correlated with adherence during actual treatment ($r = 0.50$), though adherence itself was less than perfect—70 percent during practice and 75 percent during therapy.

No single adherence strategy will work for everyone, Elion cautioned, but he proposed a general approach that should always guide clinicians—fit the antiretrovirals to the patient's lifestyle. If a regimen forces people to make many changes in their lives, he maintained, that regimen is not going to work. Factors to consider in making this fit include:

- Work and travel
- Family and children
- Dietary preferences
- Repetitive behaviors
- Habits
- Side effects considered intolerable

A study of 1,910 people found that their perception of how well a regimen fit their lifestyle directly affects adherence (Table 7).³² A 299-person survey in six cities determined what lifestyle "fitness factors" matter most.³³ The variables, ranked by order of importance, are:

- Pills per day (2 > 5 > 8 > 12)
- Dosing frequency (once a day all at same time > twice a day all at same time)
- Food rules (none > with food > empty stomach)
- Pill size (small > medium > large)
- Side effects

The once-a-day difference

The just-cited study³³ adds to the recent HIV literature indicating an adherence

Table 7. "Lifestyle-fitting" regimens and resulting adherence

Lifestyle fit	Percent adherent to therapy
Not at all	32
A little bit	46
Somewhat	50
Very well	63
Extremely well	67

$P < 0.0001$ for trend.
Source: Wenger et al.³²

advantage for once-daily versus twice-daily regimens (see Steinberg and Feinberg presentations). When Elion asked meeting delegates how many think taking pills once a day improves adherence, only about 10 percent raised their hands. He argued that a much bigger percentage of patients think so.

A December 2001-January 2002 survey of 536 people with HIV found that 80 percent thought they were likely to remember all their pills if taking them once daily, while 63 percent claimed they would miss no doses in a twice-daily regimen ($P < 0.001$).³⁴ When asked to rate their preferences of different dosing schedules, 68 percent opted for four pills once a day, 24 percent voted for one pill in the morning and two at night, and 5 percent preferred one pill in the morning and four in the evening ($P < 0.001$). A large majority of people, 73 percent, felt a once-a-day regimen would fit their daily lives better than a twice-a-day regimen ($P < 0.001$).

Elion also cited the 504-person study reviewed by Charles Steinberg showing that interest in once-daily regimens drops off as the pill count climbs past four.⁷ One convenient once-daily regimen—ddI, 3TC, and efavirenz—matched one twice-daily combination (AZT/3TC/efavirenz) and beat another (AZT/3TC/nelfinavir) in 12-month virologic efficacy.³⁵ This randomized study of treatment-naïve people found that about 80 percent in the once- and twice-daily efavirenz groups had an undetectable 12-month viral load versus 50 percent in the nelfinavir group ($P < 0.02$).

But not all once-daily drugs are created equal, as revealed in a randomized comparison of saquinavir/ritonavir (1,600/100 mg daily) and efavirenz (both with twice-daily nucleosides).³⁶ The study involved 152 treatment-naïve people with an average

CD4 count around 325 cells/mm³. An intent-to-treat analysis determined that 51 percent in the saquinavir arm and 71 percent in the efavirenz arm had a 48-week viral load below 50 copies/mL. A substantially higher rate of side effects—mostly nausea and vomiting—explained the poorer response in the saquinavir group.

When even good adherence falls short

Although staunch adherence is critical to successful therapy, there are some things adherence simply cannot do. One of those things came to light in a study of 1,420 treatment-naïve people beginning HAART in British Columbia from 1996 through 2000.³⁷ Defining good adherence as taking medications more than 95 percent of the time, researchers tracked people through March 2002 to find predictors of viral load suppression and death.

In a multivariate model *adjusted for adherence*, a pretreatment viral load above 100,000 copies/mL remained an independent predictor of death, with an adjusted hazards ratio of 1.81. To learn why, the researchers looked for differences between adherent study participants. They found that people with a baseline viral load topping 100,000 copies/mL suppressed viral replication more slowly than those with lower loads and were significantly less likely ever to reach an undetectable level. Compared with good adherers who started therapy with fewer than 50,000 copies/mL, good adherers starting with more than 100,000 copies/mL were 73 percent less likely to see viremia vanish

Therapeutic drug monitoring, or integrating antiretroviral pharmacokinetics, HIV resistance, and genetics

Eugene D. Morse
State University of New York at Buffalo

Although many European HIV clinicians consider therapeutic drug monitoring (TDM) standard of care for certain patients, antiretroviral TDM has not caught on in the United States. The reason may be low demand. When Eugene Morse asked the clinicians at the IAPAC Sessions how many had patients who asked for TDM, only a handful raised their hands. But the clinicians

themselves proved anxious to learn about measuring antiretroviral levels, grilling Morse after his talk more than any other IAPAC Sessions presenter.

The ABCs of pharmacokinetics (PKs)

The potential for unwanted drug interactions is the main reason for interest in TDM, Morse said. He counted 21 antiretroviral formulations in the United States, and the recently approved 625-mg nelfinavir tablet makes it 22. A salvage regimen might include two ritonavir-boosted PIs, an NNRTI, and a few nucleosides, or tenofovir, or even enfuvirtide (T-20). Add to that mix the medications taken for comorbidities, not to mention herbal remedies the clinician may or may not know about, and potential interactions escalate.

Most TDM research has focused on protease inhibitors because (1) measuring active triphosphates of nucleosides inside cells remains difficult, and (2) nonnucleosides typically reach high concentrations and have long half-lives. But whether it's better to gauge one drug level or another—trough, peak, or area under the curve—has not been determined (Figure 2).

Measuring levels of PIs and NNRTIs is complicated by protein binding, which decreases the amount of free drug available to inhibit HIV (Figure 3). Free drug is what TDM sizes up, for example, when determining a trough. Inhibitory concentrations, to assess viral susceptibility to the drug, also reflect free drug. The inhibitory quotient (IQ) is typically determined by dividing the trough by a 50 percent inhibitory concentration (IC₅₀). Because both values are derived from free drug, the equation must be "corrected" by some preset protein binding factor.

The potential value of the IQ lies in its integration of drug exposure with viral susceptibility. So far research on lopinavir, indinavir, amprenavir, and saquinavir has identified a relationship between the IQ and viral suppression. No prospective data verify improved outcomes as a result of IQ monitoring, Morse noted, although such studies are under way. Two AIDS Clinical Trials Group (ACTG) studies will assess the normalized IQ (NIQ), which skirts the protein-binding pitfall by placing a "reference IQ" in the denominator:

$$NIQ = \frac{\text{patient IQ}}{\text{reference IQ}}$$

(Reference IQ = population trough concentration/wild type IC₅₀)

Figure 2. The major antiretroviral pharmacokinetic variables now include the inhibitory quotient (IQ), usually defined as the trough concentration divided by the 50 percent inhibitory concentration (IC_{50}).

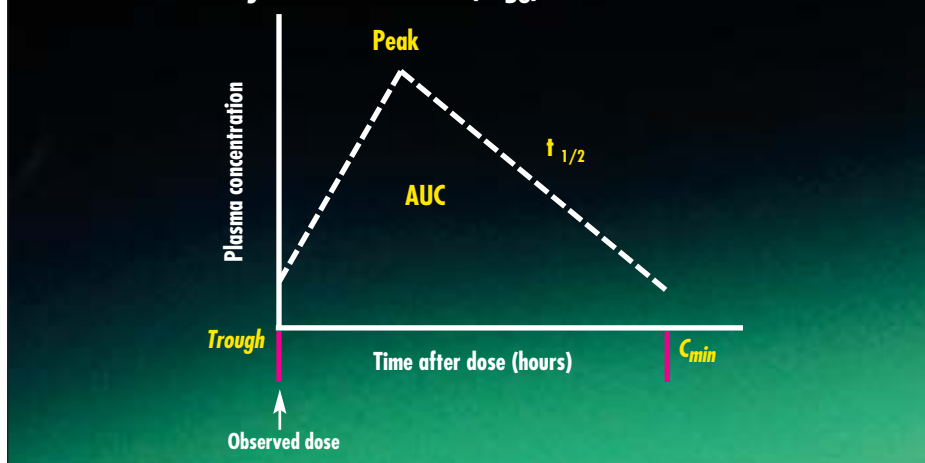
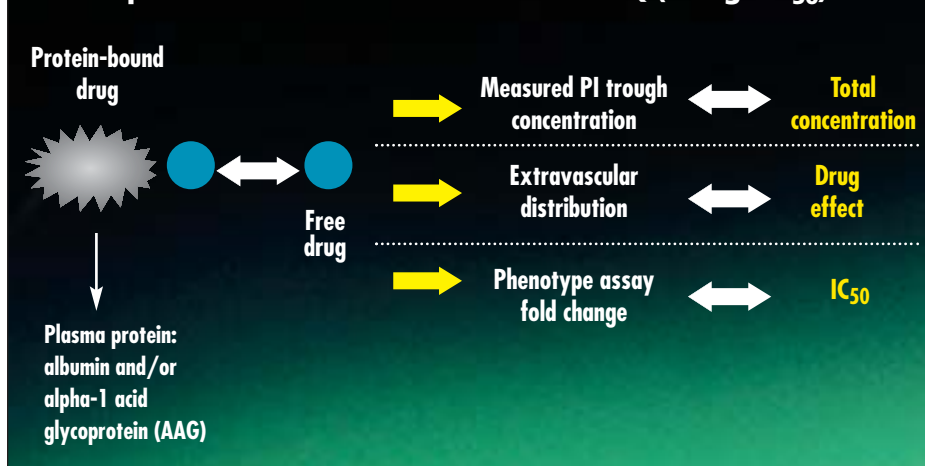


Figure 3. Binding of antiretrovirals to plasma proteins limits the amount of free drug available to inhibit HIV and affects pharmacokinetic values such as the IQ (trough/ IC_{50}).



Protein binding is only one variable that frustrates the simple reckoning of drug-drug interactions involving antiretrovirals. Pharmacologists must also consider sped-up or slowed-down drug metabolism by the liver. But before drug even gets to the liver, it may be thwarted by efflux pumps such as P-glycoprotein (P-gp), which affects antiretroviral absorption via the gut and penetration of cerebrospinal fluid (CSF) and T cells. Intracellular interactions also influence drug levels in CSF, semen, and other sites.

These variables have different effects on different antiretrovirals. Indinavir, for example, attains good semen-to-blood plasma and lymph node-to-plasma ratios, while nelfinavir and lopinavir do not.³⁸ Indinavir also penetrates CSF better than nelfinavir or lopinavir.

Genes regulate all of these mechanisms. Polymorphisms in genes controlling cytochrome P450 isoforms can influence drug metabolism. Polymorphisms in the *MDR-1* gene, which controls P-gp, can change drug absorption and distribution.

Boosting PIs with low-dose ritonavir has smoothed out spikey drug level curves. But the lofty and durable curves seen in PK study slides don't tell the whole story, Morse warned. If you add confidence intervals around each data point, it becomes clear that not all patients attain the average high concentration. And ritonavir-boost studies rarely show the effects of other drug interactions.

Why do TDM—and where?

Confounders like those reviewed in the preceding section inspire caution about

the wholesale use of TDM in clinical practice. But the fundamental rationale for checking drug levels is sturdy:

- Data suggest a concentration-response relation for PIs and NNRTIs.
- Complex drug interactions may alter plasma concentrations.
- Measuring those concentrations—TDM—may help individuals attain desired drug exposure.

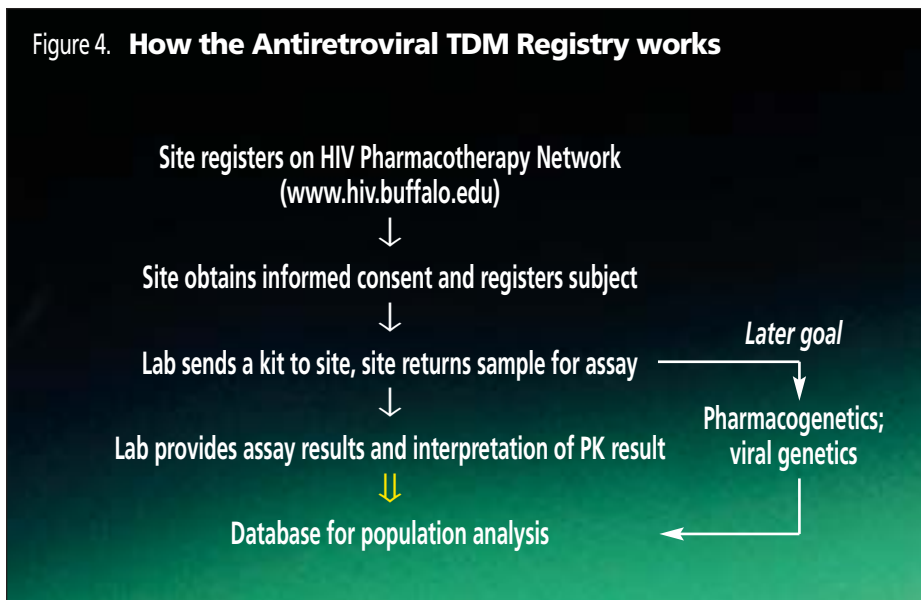
The principal trial underpinning the value of TDM, though convincing, has its limits. The TDM study of the ATHENA cohort randomized people starting nelfinavir or indinavir to have drug level results, and advice, reported to their clinicians, or to have TDM but not have results reported.³⁹ The findings may have diminished applicability because everyone was treatment-naïve when the study began, and because the unboosted PIs studied are used less often now than when the trial began. But 12 months of follow-up showed that TDM did what it's supposed to do.

The study involved 92 people taking nelfinavir and 55 taking indinavir. Whereas 17.4 percent randomized to the TDM group discontinued one of the PIs by month 12, 39.7 percent in the control group did so. Among people taking nelfinavir, 2.4 percent in the TDM group versus 17.6 percent in the control group had virologic failure. In the indinavir arm, toxicity affected 14.3 percent in the TDM group and 29.6 percent of controls. According to a noncompleter-equals-failure analysis, significantly more people in the TDM group (78.2 percent) than in the control group (55.1 percent) had a 12-month viral load below 500 copies/mL.

Where can a US clinician send a sample for TDM? A few commercial labs and medical centers offer the service, Morse said, but many have no proficiency testing. A TDM lab must also be CLIA certified and should be able to report results promptly. (CLIA stands for Clinical Laboratory Improvement Amendments, administered by the Centers for Disease Control.)

Six ACTG sites perform TDM and have proficiency testing—Johns Hopkins, Stanford, the University of Alabama at Birmingham, the University of California, San Francisco, the University of Colorado, and Morse's team at the State University of New York at Buffalo. Although the

Figure 4. **How the Antiretroviral TDM Registry works**



Buffalo group will accept samples from approved sites as part of a research protocol, Morse could not speak for the other sites.

The Buffalo Antiretroviral TDM Registry has three goals:

1. Establish a clinical research mechanism for measuring PIs and NNRTIs in HIV-infected individuals after informed consent.
2. Implement a Web-based registry to collect data on adherence and concurrent medications during pharmacotherapy with complex antiretroviral regimens.
3. Provide a reporting mechanism to the sites for assay results.

Figure 4 outlines how the registry works. TDM will be done on samples from anyone taking a PI or NNRTI who meets one of the following criteria:

- Suspected additional drug interaction with the antiretroviral regimen
- Suspected factor associated with insufficient or excessive PI or NNRTI concentrations (such as malabsorption, achlorhydria, or renal dysfunction)
- Coinfection with hepatitis B or C virus
- Failure of initial antiretroviral regimen
- Suboptimal virologic response in an adherent patient
- Suspected antiretroviral toxicity

Twelve sites are already slated to be phased in to the registry (see note 40). Ultimately, Morse hopes the registry will provide a 3,000-patient PI and NNRTI database that can be queried regularly

to address concerns involving TDM, drug interactions, resistance, toxicity, and polymorphisms affecting antiretroviral pharmacokinetics.

Morse is gradually making TDM a routine part of HIV disease care in his clinic by linking it with resistance testing. A panel of clinicians had already been meeting regularly to discuss resistance test results from people cared for at the clinic. Morse encouraged his colleagues to order a drug level every time they order a resistance test, and now the panel discusses both results at the same time. Most of the people who have had TDM at Buffalo are taking complex rescue regimens.

Session chair Mark Dybul (National Institute of Allergy and Infectious Diseases, Bethesda) suggested the Buffalo model may be a way to integrate TDM into routine care, at least at medical centers or large practices. Dybul himself has ordered TDM for some patients and typically calls a few HIV pharmacologists to help him interpret the results.

A hurdle to TDM interpretation is the lack of formally established high or low concentration cutoffs for each agent, a task complicated by the proliferation of ritonavir-boost doses. At least two cutoff schemes have been proposed, one by the editorial board of HIVPharmacology.com⁴¹ and the other by University of Alabama pharmacologists Edward Acosta and Jennifer King.⁴² Morse cautioned that cutoff determinations often rely on data derived from people taking their first antiretrovirals and so may not be valid for people with heavy treatment experience.

Which patients are good candidates for TDM? Several groups have proposed lists, including an international panel of HIV pharmacologists and clinicians headed by the University of Liverpool's David Back.⁴³ Mark Dybul proposed the following list for Morse's review:

- Suspected drug-drug or drug-food interactions
- States that impair hepatic, gastrointestinal, or renal function
- Possible sensitivity to high doses in antiretroviral-experienced persons
- Suspected drug-associated toxicities
- Lack of response in a person starting a first regimen

If using TDM to check adherence, which may be the problem in Dybul's fifth scenario, Morse suggested getting a morning trough level then comparing it with a trough after an observed dose. He also proposed three more TDM candidates:

- Patients at extremes of body weight
- Women approaching menopause
- People taking a once-daily boosted PI

The international panel's long list⁴³ included most of these, as well as:

- Pregnancy
- Childhood
- Use of more than two drugs that influence cytochrome P450 activity
- Change in clinical or physiological status suspected of causing abnormal drug levels
- Dose intensification of failing regimens
- Deep salvage therapy (even with ritonavir boosting)

Yet Morse reminded delegates that evidence supporting the clinical value of resistance testing remains thin. Because of intraindividual variation in drug levels, you can't be certain that a level will be the same the next time you measure it, even if you don't change the dose. And if you do change the dose, you can't be certain the drug level will also change.

Geno, pheno, and virtual pheno: Which patient needs what (and why)?

*David A. Katzenstein
Stanford University School of Medicine*

The panel that writes antiretroviral guidelines for the Department of Health and Human Services (HHS) is pondering a change in advice on resistance testing. At the time of the IAPAC Sessions, the HHS guidelines recommended resistance testing only in people with virologic failure or suboptimal suppression of viral load after starting antiretrovirals.⁴⁴ Those guidelines say testing should be “considered” before starting therapy in someone with acute HIV infection, but that scenario may be bumped up into the “recommended” category. At the time of the IAPAC Sessions, the HHS labeled resistance testing “not generally recommended” before starting therapy in someone with chronic HIV infection. That scenario may be promoted to the “considered” category.

But most clinicians attending the IAPAC Sessions seem to be taking their cue not from the HHS but from the British HIV Association, which thinks people with chronic infection should have a pretreatment resistance test.⁴⁵ The HHS panel justified its reluctance to endorse pretreatment testing during chronic infection by noting that resistance mutations tend to fade to undetectable minorities in someone not taking antiretrovirals. That wasn't the rationale offered by the single IAPAC Sessions delegate who spoke against testing in such patients, arguing that it's “crazy” in the current economic climate. The county where he works has already twice run out of resistance test vouchers, so he believes the tests should be reserved for those who stand the best chance of benefiting.

Delegate opinion was more mixed on the value of ordering a resistance assay for an untreated person with acute infection. David Katzenstein maintained that the clinical benefit of testing in acute infection remains unproved, noting that reports of virologic failure resulting from primary infection with resistant virus have been rare. IAPAC Sessions Co-Chair Diane Havlir, on the other hand, worried that failure to test acutely infected people would make it impossible to spot the potential emergence of multidrug-resistant virus.

Other clinicians in the room proposed that decisions on testing people with acute infection should be based on the prevalence of resistance transmission in that region. A physician from North Carolina, for example, found almost no cases of resistance in 40 patients with acute infection, most of whom lived in rural areas. But

another clinician from Orlando, Florida, said transmission of resistant HIV is not uncommon there.

Virtues and vagaries of genotyping

The virtue of genotyping is that it gives a straightforward result, detecting at least majority populations of mutants that confer resistance to specific drugs. Then the difficulties begin, Katzenstein lamented, because interpreting genotypes can be tough. Certain mutants have complex effects on some drugs—but not others. Expert algorithms often disagree on what a complicated mutation set means.

In a Utopian world stripped of all confounders, interpreting a genotype would yield a clear prediction of viral susceptibility to antiretrovirals of interest. Knowing precisely which drugs or classes would stifle a patient's virus, the clinician could then decide on a course of action:

- Reinforce adherence.
- Modify a single drug in the regimen.
- Add one or more drugs.
- Switch drugs.
- Boost a drug.

For some drugs—such as abacavir, tenofovir, and lopinavir—knowing which mutants dominate a person's viral population tells the clinician a lot. A study of people beginning abacavir found that 85 percent of those with wild-type (nonmutant) virus had more than a half-log drop in viral load or an undetectable load after 12 weeks of treatment.⁴⁶ With one or two mutations conferring resistance to AZT, the response rate fell to 77 percent. With one or two AZT mutations plus the 3TC-inspired 184V change, the response rate dipped to 60 percent. Three or more AZT mutations, and three or more AZT mutations plus 184V, trimmed the response rate even more. But other work suggests that 184V alone increases susceptibility to the thymidine analogs, AZT and d4T.^{47,48}

A study of people beginning tenofovir found the best 24-week response in those with no AZT/d4T mutations, a lessened response in those with one or two, and little response in those with three AZT/d4T mutations including 41L or 210W.⁴⁹ Abbott researchers demonstrated different 24-week response rates to lopinavir/ritonavir depending on whether people began treatment with zero to five PI mutations, six or seven PI mutations, or eight to 10 PI mutations.⁵⁰

Studies like these may clarify the effect of discrete mutations or mutation sets on the probability that a person will respond to certain drugs. But, Katzenstein asked, can such information be readily adapted to clinical practice? Genotypes can be translated into treatment advice in three ways—by a rules-based algorithm, by expert opinion, or by a database comparison (as with the VirtualPhenotype, described below).

Algorithms are fallible because the experts who build them cannot be infallible. A study comparing four often-used algorithms made that abundantly clear.⁵¹ Feeding 2,045 viral sequences into the four decision trees, Katzenstein's colleague Robert Shafer charted which sequences the algorithms rate sensitive, intermediate, or resistant to given drugs. He found complete concordance for only 66.4 percent of interpretations, and most of those concordant calls involved sensitive virus. While 15.4 percent of interpretations disagreed on sensitive-versus-intermediate calls, 13.8 percent involved intermediate-versus-resistant discordance.

On another 4.4 percent of interpretations, algorithms disagreed on whether a sequence was sensitive or resistant to some drugs. For example, two algorithms called virus with reverse transcriptase mutations 74V, 184V, and 215F or Y sensitive to d4T, one called it resistant, and one called it intermediate. Two algorithms predicted that virus with the protease changes 84V plus 90M would be resistant to amprenavir, one called it sensitive, and another called it intermediate.

Virco's VirtualPhenotype estimates the likely susceptibility of a submitted genotype by searching its database of phenotyped viral samples with the same genotype. A comparison of the VirtualPhenotype and real phenotyping in 201 heavily pretreated people found that the two tests performed similarly in picking new suppressive regimens.⁵² After 48 weeks of follow-up, people randomized to real phenotyping had virtually the same virologic responses as people randomized to the VirtualPhenotype (Table 8). One way of interpreting these results, Katzenstein offered, is that a VirtualPhenotype will add no valuable new information to a real phenotype.

Possible progress with phenotyping

Randomized, controlled trials comparing genotyping with standard of care show a consistent, if often small and short-term

Table 8. Virologic responses 48 weeks after a real phenotype or VirtualPhenotype

48-week response	Real phenotype	Virtual-Phenotype
Viral load below 50 copies/mL (%)	20	24
Viral load decrease by more than 0.5 log (%)	58	61
Mean viral load decrease (log copies/mL)	0.92	0.94
CD4-cell increase (cells/mm ³)	42	94

None of the differences are statistically significant.

Source: Mazzotta et al.⁵²

virologic benefit with testing. The genotyped groups in four trials⁵³⁻⁵⁶ all had better average 12-week responses than the standard-of-care groups, ranging from a 0.48-log improvement in VIRADAPT⁵³ to a 0.18-log improvement in ARGENTA.⁵⁴

Results in phenotyping trials have been mixed. VIRA 3001 found an average 0.37-log 12-week advantage for phenotyping over standard of care,⁵⁷ but NARVAL⁵⁸ and CCTG 575⁵⁹ found no benefit with phenotyping. (Two other randomized trials not reviewed by Katzenstein also differed on whether phenotyping can help pick a new regimen.^{60,61}) The varying results of phenotyping trials can be partly explained by different study designs, different populations, and recent approval of more drugs that counter some resistant virus.

As with genotyping, though, phenotyping cannot yield certain conclusions because the assays—and their interpretation—are imperfect. A phenotypic assay measures how much drug one needs to inhibit replication of a virus by 50 percent, the IC₅₀. That value is then compared with the drug's IC₅₀ against wild-type virus to yield a “fold change” in viral susceptibility to the drug. But it's not so easy to set IC₅₀ cutoffs that signal when a drug will be active, inactive, or partially active against a virus.

Katzenstein and colleagues tried to improve the reliability of phenotyping by toting a continuous—rather than dichotomous—phenotypic sensitivity score (PSS). Resistance, he explained, is usually not a dichotomous, black-or-white phenomenon. It is a continuous variable that changes as

the viral population evolves, embracing greater or lesser proportions of sensitive and resistant virus.

A dichotomous PSS can be figured by assigning a value of 1 to each drug in a regimen against which the virus has a 2.5-fold or less change in susceptibility compared with wild-type virus (or 1.5-fold or less for ddI and d4T). Drugs score 0 if the fold change exceeds 2.5. The scores for each drug in the regimen get added up to yield the dichotomous PSS.

A continuous PSS attempts to account for gray areas in viral susceptibility by adding some flourish to the homely dichotomous equation. Again, each drug scores 1 if the fold change is 2.5 or less (or 1.5 or less for ddI and d4T). If the fold change tops 10, the drug scores 0. For fold changes between 2.5 and 10 (or 1.5 and 10 for ddI and d4T), a value between 0 and 1 is calculated thus:

$$1 - (\text{fold change} - 2.5) / \text{fold change}$$

Katzenstein retrospectively tested the continuous PSS in viral samples from ACTG 364, which enrolled 195 people with only nucleoside experience and randomized them to nelfinavir, efavirenz, or both plus two nucleosides.⁶² Everyone began the new regimen with a viral load above 2,000 copies/mL.

Defining virologic failure as a confirmed viral load of 2,000 copies/mL or more at week 16 or later, the ACTG team found that a PSS of 3 or more correlated with durable suppression of viremia through 144 weeks. In the group with a PSS at or above 3, the proportion remaining free of virologic failure stayed steady after week 24 at about 80 percent. In the group whose PSS lay between 2 and 3, the proportion free of virologic failure fell steadily over the study period, ending up near 40 percent. And in the group with a PSS of 2 or less, only 20 percent had escaped virologic failure by week 144.

Katzenstein concluded that an effective rescue regimen must contain at least three “fully active” drugs or the continuous PSS equivalent of 3. He told IAPAC Sessions delegates that he believes the future of clinical resistance testing will involve a measure like the continuous PSS, but he cautioned that this formula—and any resistance formula humans devise—has its limits. Although it is more elastic than a dichotomous PSS, the continuous ver-

sion must still rely on cutoffs that cannot accurately reflect viral susceptibility for every individual. The ACTG 364 PSS analysis does improve on earlier resistance assay trials in length of follow-up, but the analysis was retrospective.

Finally, Katzenstein urged his clinician colleagues to remember that “resistance is a relatively small part of a large picture—maintaining a clinically effective treatment strategy.” With that perspective in mind, he suggested the following approach to interpreting resistance tests.

1. Use the test results to rank drugs from the most potentially active to the least.
2. Consider other key variables, including history, toxicities, adherence, CD4 count, and viral load.
3. Review potential regimens for possible pharmacologic interactions—good and bad.
4. Consider potential mutational interactions and viral fitness.

Keys to controlling lipids, insulin, and glucose

*Colleen M. Hadigan
Massachusetts General Hospital
Boston*

Introducing the two talks on metabolic abnormalities in people with HIV, Kathleen Mulligan (University of California, San Francisco) posed a question that captured some key conflicts in this field:

Can we study it and manage it even if we can't agree on what to call it, how to define it, or what causes it?

The answer appears to be a qualified yes, if one can judge from the volume of work done on the metabolic complications of HIV and antiretrovirals, and from some progress in controlling them. And a definition of lipodystrophy has been proposed, although results of a large case-control study of fat abnormalities in people with and without HIV infection^{63,64} don't agree with the first rigorous case definition based on a case-control study of HIV-infected adults with or without apparent symptoms.⁶⁵ “We now have a case definition,” Mulligan noted. “I'm not going to say we have consensus.”

The case definition uses a scoring system incorporating 10 variables. Clinicians

can access an interactive online program of that definition or of two simpler versions, plug in numbers from their patients, and see if they meet the case definition.⁶⁶ But IAPAC Sessions delegates apparently saw little value in that exercise, since none had done so. One veteran HIV clinician explained his lack of enthusiasm by pointing to the case definition study's design. "A sophisticated regression model like that won't help me decide on the borderline cases," he said. By eliminating people with iffy lipodystrophy, the study eliminated the very people who interest him most. "I already know which people have severe lipodystrophy."

Mulligan listed HIV-related metabolic and morphologic abnormalities in four separate boxes:

- Disorders of glucose metabolism
- Disorders of lipid metabolism
- Central fat accumulation
- Peripheral fat loss

Can the boxes be connected, she asked. If the boxes overlap, can distinct phenotypes still be defined? Are antiretrovirals or host factors more to blame? What is their long-term clinical significance? And what's the best way to manage them? The two speakers at this session—Colleen Hadigan and Morris Schambelan—didn't have all the answers. But they suggested more than a few.

Prevalence of metabolic abnormalities

Hadigan started by asking two questions of her own:

1. What is the prevalence of diabetes in HIV-infected people with fat abnormalities?
 - a) 1 percent
 - b) 7 percent
 - c) 23 percent
 - d) 57 percent
2. What is the prevalence of hyperlipidemia in people taking HAART?
 - a) 1 percent
 - b) 7 percent
 - c) 23 percent
 - d) 57 percent

Most delegates picked the right answers before Hadigan reviewed studies that yielded remarkably consistent numbers. Her own work found that 7 percent of 71

people with changes in body fat met World Health Organization criteria for diabetes, and 35 percent had impaired glucose tolerance.⁶⁷ An Australian study charted the same diabetes prevalence in 113 people taking a protease inhibitor.⁶⁸ And Spanish clinicians found that 5.8 percent of PI-treated men with lipodystrophy had diabetes.⁶⁹

In Hadigan's study 57 percent had fasting triglycerides above 200 mg/dL; the same proportion had cholesterol readings above 200 mg/dL.⁶⁷ This case-control analysis found significantly higher proportions with hyperglycemia, hypercholesterolemia, hypertriglyceridemia, and decreased high-density lipoprotein cholesterol (HDL-C) in the 71 people with HIV and lipodystrophy than in the 213 HIV-uninfected controls ($P < 0.03$). Thirty HIV-infected people without lipodystrophy had a metabolic profile similar to that of 90 controls, except that about 40 percent in the HIV group had an HDL-C below 35 mg/dL compared with about 5 percent of controls ($P < 0.01$). A review involving 159 Australian men with HIV found triglycerides above 177 mg/dL in 52 percent and high cholesterol in 44 percent, regardless of fat distribution.⁷⁰

A study of 1,927 children with HIV infection counted 22 percent with cholesterol levels above 200 mg/dL compared with 9 percent of HIV-uninfected but perinatally exposed controls.⁷¹ In the HIV group 12 percent had a cholesterol tally above the 95th percentile for healthy children. The researchers linked these high cholesterol levels to PI use, adherence to therapy, and younger age. Nonnucleosides had a protective effect. With effective antiviral therapy, Hadigan observed, these children will have lived with high lipids for 20 years by the time they're young adults.

Comparing 91 HIV-infected men and women with 273 age-, sex-, and body mass index-matched controls without HIV, Hadigan learned that 46 percent in the HIV group met criteria for the metabolic syndrome (see note 72) versus 15 percent of controls ($P = 0.001$).⁷³ Nearly 30 percent of the people with HIV had more than a 10 percent risk of cardiovascular disease in 10 years versus fewer than 15 percent of controls ($P = 0.001$).

What upsets metabolic measures in people with HIV infection?

An array of research in the past few years

implicates certain antiretrovirals in insulin resistance, dyslipidemia, and adipocyte abnormalities. Hadigan offered this outline:

- Antiretrovirals affect glucose utilization and lipid production and clearance.
- Antiretrovirals increase rates of lipolysis.
- Antiretrovirals affect adipocytes through dysregulation of the transcription factors PPAR-gamma and SREBP-1 and perhaps through mitochondrial toxicity.

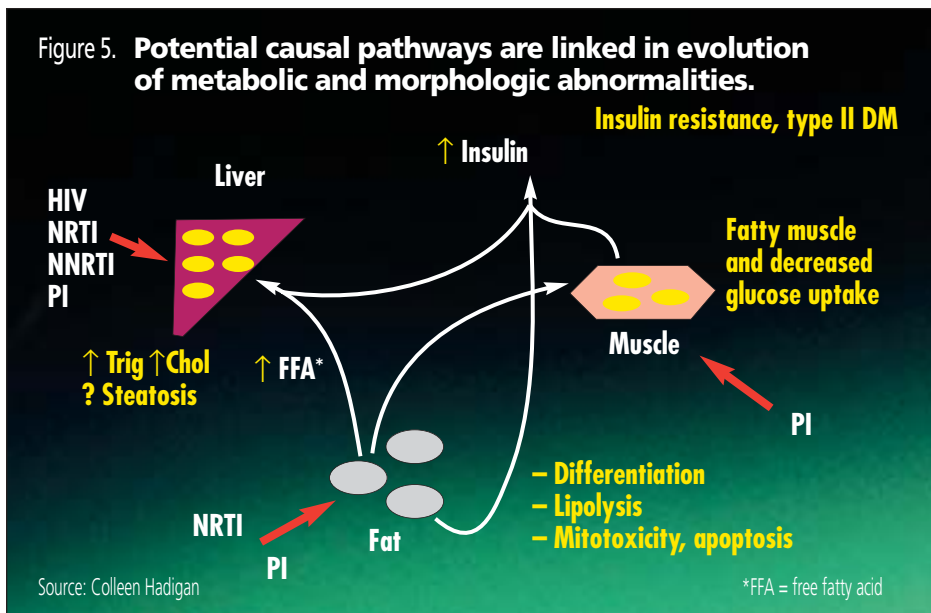
Researchers at Washington University in St. Louis determined that indinavir, ritonavir, and amprenavir squelch insulin-stimulated glucose uptake in adipocytes by inhibiting the glucose transporter GLUT-4.⁷⁴ Morris Schambelan's group showed that a single dose of indinavir decreases insulin sensitivity in healthy men without HIV infection.⁷⁵ Last year a study of ritonavir-fed mice traced a 30 percent jump in very low-density lipoprotein (VLDL) cholesterol.⁷⁶ That increase doubled when the mice also ate a high-fat diet. HIV alone boosted hepatic production of VLDL apolipoprotein B, and either PI therapy or NNRTI therapy reduced its clearance.⁷⁷

Nelfinavir increases lipolysis—the release of fatty acids from adipocytes into the circulation—in a dose-dependent manner.⁷⁸ Hadigan found higher rates of lipolysis in 19 people with HIV than in eight uninfected controls; and d4T upped that rate regardless of treatment with a PI.⁷⁹ Levels of adipogenic transcription factors SREBP-1 and PPAR-gamma proved significantly higher in 26 people taking antiretrovirals than in 18 uninfected controls.⁸⁰ Everyone in this study was taking a PI, and most were taking d4T.

ACTG 384 charted declines in limb fat after 16 weeks of therapy with regimens containing either AZT/3TC or ddI/d4T, although the drops were significantly greater in the ddI/d4T group ($P < 0.05$).⁸¹ Some recent work attributes peripheral lipodystrophy to nucleoside-induced mitochondrial toxicity, but Hadigan doesn't think the case has been clinched.

Bravely, she attempted to summarize much of this mechanistic research in a single slide outlining the effects of HIV and antiretrovirals on the liver, of PIs and nucleosides on fat cells, and of PIs on muscle (Figure 5). Perhaps her most important point was that the effects on fat and metabolic variables cannot be separated.

Figure 5. **Potential causal pathways are linked in evolution of metabolic and morphologic abnormalities.**



Two-pronged approach to management

Hadigan reviewed work suggesting two approaches to managing metabolic complications:

- Stop the offending agent (if it can be identified)
- Treat the metabolic complications

Several studies show that replacing d4T (and sometimes a PI) with another nucleoside (and the PI with abacavir) can slowly but measurably reverse peripheral lipoatrophy.⁸²⁻⁸⁶ Most recently, a study of 13 people who swapped d4T for abacavir or AZT graphed gains in arm, leg, and trunk fat of 25 percent, 15 percent, and 23 percent.⁸⁷ Adipocyte apoptosis, perhaps driven by mitochondrial toxicity, waned after people stopped d4T.

The protease inhibitor atazanavir may have an advantage over other PIs even greater than its once-daily dosing. Several trials convincingly show that atazanavir barely affects—and sometimes improves—lipid parameters. A published study that compared atazanavir with nelfinavir for 48 weeks in treatment-naïve people found 20 percent to 40 percent gains in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides with nelfinavir, but little change with different doses of atazanavir.⁸⁸ Portentous LDL-C dropped in the group taking 400 mg of atazanavir.

The safest lipid-lowering therapy, diet, works in people taking PIs. A Spanish study of people with elevated lipids found that a low saturated fat diet dropped

triglycerides by 50 percent and cholesterol by more than 20 percent in PI takers who stuck with the diet.⁸⁹ Lipid levels fell only modestly in people not taking PIs.

A 12-week trial of diet with or without gemfibrozil in PI-treated people with lipodystrophy and high triglycerides found a nonsignificant improvement in triglycerides in the gemfibrozil group versus the diet-only group ($P = 0.06$).⁹⁰ Only one person reached a normal triglyceride level, and gemfibrozil did not change cholesterol, HDL-C, glucose, or insulin.

Niacin extended-release tablets significantly lowered but did not normalize triglycerides and cholesterol in 14 HIV-infected men with high triglycerides or LDL-C.⁹¹ Although no one suffered a grade 3 or 4 liver function test elevation in the 14-week study, indicators of insulin sensitivity worsened.

Atorvastatin and pravastatin are the preferred anticholesterol agents for people taking PIs because protease drugs drive simvastatin and lovastatin levels to dangerously high reaches. Early studies of atorvastatin and pravastatin in antiretroviral-treated people with high lipids show some drops in lipids, but usually not into normal ranges.⁹²⁻⁹⁴ When statins fall short, a fibrate may be added, but at the risk of liver toxicity and rhabdomyolysis.

Hadigan studied metformin at a dose of 500 mg twice daily in 25 HIV-infected people with a waist-to-hip ratio above 0.9 and insulin levels exceeding 15 $\mu\text{U/mL}$.⁹⁵ After 12 weeks insulin area under the curve had dropped significantly in the metformin group compared with the

control group ($P = 0.01$). Mean weight and waist circumference also improved significantly with metformin while rising with placebo.

Metformin decreased visceral adipose tissue in another study of people taking PIs,⁹⁶ but it also cut subcutaneous fat in both studies, so it may worsen peripheral lipoatrophy. Other potential side effects of metformin are diarrhea and hyperlactatemia. Hadigan added that a just-completed study by her group charted an additive effect of metformin and exercise on strength, body composition, and insulin sensitivity.

A study of the thiazolidinedione troglitazone in people with non-HIV congenital lipodystrophy showed that it increases thigh and abdominal subcutaneous tissue while lowering visceral fat.⁹⁷ When troglitazone got pulled from the market because of liver toxicity, research attention shifted to rosiglitazone and pioglitazone. The first placebo-controlled trial of rosiglitazone found improved liver function tests and decreased liver fat after 24 weeks in the active treatment group, along with improved insulin.⁹⁸ But subcutaneous fat did not increase significantly, and triglycerides did.

A smaller, nonrandomized study found that six to 12 weeks of rosiglitazone increased subcutaneous fat by 23 percent ($P = 0.05$) and cut visceral fat by 21 percent ($P = 0.04$) in HIV-infected people with insulin resistance.⁹⁹ Glucose disposal also improved, but lipids rose.

Beyond considering switching antiretrovirals or adding drugs to counter their side effects, Hadigan said, getting people to stop smoking will probably do more to lower their cardiovascular risk.

Fat in all the wrong places

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Fat abnormalities in people with HIV began appearing before they started taking protease inhibitors, as Morris Schambelan learned in the mid-1990s. That's when his colleagues started referring HIV-infected patients to see if their buffalo humps might mean they had Cushing's disease. In eight people referred between June 1995 and October 1997, Schambelan ruled out Cushing's, discovering instead a fat change specific to people with HIV.¹⁰⁰

With body mass indices (BMIs) averaging 24.7 kg/m², these eight people were not obese. And their CD4 counts were not remarkably low. But they had had a buffalo hump for one to 26 months. Compared with 15 age-, CD4 count-, and BMI-matched controls, they had significantly more trunk fat as a percentage of total fat (65.3 versus 56.8 percent, *P* = 0.03). Three of them were taking indinavir and one nelfinavir, but the other four were taking only one or two nucleosides. This early study of fat accumulation in antiretroviral-treated people made it plain that PIs were at most a contributing factor.

Antiretrovirals and visceral versus limb fat

The arrival of protease inhibitors did have an impact on body fat. Comparing body measures in people who switched from AZT/3TC to ddI, d4T, and nelfinavir, Schambelan saw almost no change in overall weight (Table 9). But DEXA-measured total fat fell after nine months of the new regimen, trunk fat increased, and peripheral fat fell. Visceral adipose tissue rose, while subcutaneous adipose tissue dropped. What this kind of analysis cannot sort out is the cumulative effect of nucleosides or the independent effect of changing from AZT/3TC to ddI/d4T.

Central fat certainly piles up with age, as Schambelan demonstrated with a photo of the sleek 1936 Olympic gold medal rowing crew and a 50th reunion shot of these same, now uniformly rotund, fellows. Research confirms that visceral fat adds up as the years pass by in both men (*r* = 0.66, *P* = 0.007) and women (*r* = 0.68, *P* = 0.001).¹⁰¹ But sudden and rapid abdominal enlargement, reflecting up to a 30 percent gain in visceral adipose tissue, is not the same as the waist widening that comes with age.

Explaining central girth gains in people taking antiretrovirals remains difficult, as the FRAM study shows.^{63,64} The loss of peripheral fat, on the other hand, has been linked convincingly to antiretroviral therapy. Schambelan and Kathleen Mulligan offered one of the clearest demonstrations of antiretroviral effects on limb fat in a cross-sectional comparison of 44 people without HIV infection, 23 HIV-infected but untreated people, 30 people taking only NRTIs, and 26 taking NRTIs plus a PI.¹⁰²

Table 9. **Body composition changes after a switch to a PI regimen**

	September 1999 AZT/3TC	June 2000 ddI/d4T/ nelfinavir
Duration of therapy (m)	36	9
Weight (kg)	79.2	79.8
Total fat by DEXA (kg)	17.9	17.3
Trunk fat by DEXA (kg)	12.3	13.8
Appendicular fat by DEXA (kg)	4.7	2.8
Visceral adipose tissue by CT (mm ²)	30,734	40,319
Subcutaneous adipose tissue by CT (mm ²)	14,668	10,556
Waist (cm)	96.5	98.1
Hip (cm)	95.6	93.3
Midthigh (cm)	44.8	42.3

Mulligan and Schambelan found that the treated groups did not differ significantly from the untreated and uninfected groups in trunk fat divided by height. But the people taking antiretrovirals had significantly less limb fat per height than the two control groups and a significantly higher trunk-to-limb fat ratio. The NRTI-only group did not differ from the NRTI/PI group in either of these two measures.

Some evidence suggests, though, that nucleosides and protease inhibitors have an additive effect on limb fat loss. Most recently, Schambelan noted, limb fat proved significantly lower in treatment-naive people randomized to take nelfinavir than in those randomized to efavirenz in ACTG 384.⁸¹

Does mitochondrial toxicity drive lipoatrophy?

Mitochondrial DNA depletion in fat cells and elsewhere among people taking nucleosides has buttressed the theory that lipoatrophy is a nucleoside-induced mitochondrial toxicity. But some researchers, including Colleen Hadigan, are not yet swayed by these arguments. The tissue of interest is not fat, she observed in an open discussion, but muscle, where mitochondrial function is critical.

A study by Schambelan's group addressed the role of mitochondria in muscle of eight people with severe peripheral lipoatrophy and eight antiretroviral-treated controls without atrophy.¹⁰³ Although

mitochondrial damage has been noted in muscle of people with lipoatrophy, Schambelan's group wanted to know what the functional consequences may be. The atrophy group was significantly older than controls, but the groups didn't differ in body mass index, CD4 count, duration of HIV infection, or current PI or NNRTI use.

Measuring subcutaneous fat in the right calf, thigh, and gluteal region by MRI, Schambelan's team found significantly less in all three areas among the people with clinically apparent atrophy (*P* < 0.001 for all comparisons). Although the atrophic patients had less DEXA-measured total body fat and limb fat than controls, their total and appendicular lean body mass proved equivalent with controls. In other words the people with atrophy did not have muscle wasting.

Next Schambelan and colleagues compared measures of the tibialis anterior muscle (which makes the foot tap) in cases and controls. They found no significant differences in cross-sectional area, maximal voluntary contraction, or specific strength. Phosphocreatine recovery after exercise proved virtually identical in the two groups, another finding indicating no difference in muscle function. Finally, with study participants at rest, the researchers looked at muscle metabolites that might signal worse muscle function; they found no differences between the two groups.

Although the study was small, Schambelan concluded that people with severe peripheral lipoatrophy do not differ from antiretroviral-treated people without atrophy in muscle-specific strength, intramuscular energy metabolism, or indices of mitochondrial function.

Does fat atrophy add to insulin resistance?

Schambelan suggested three lines of evidence suggesting that fat loss in people taking antiretrovirals contributes to insulin resistance in some of these people:

1. Most forms of classic inherited or acquired lipoatrophy in people without HIV infection are associated with profound insulin resistance.
2. The degree of insulin resistance correlates with a lack of limb fat in HIV-infected people.
3. Severe insulin resistance occurs in transgenic mice lacking fat.

A study comparing 15 HIV-infected

people with lipoatrophy, 14 HIV-infected people without atrophy, and 12 healthy controls established the correlation between low limb fat and insulin resistance among people with HIV.¹⁰⁴ The gold-standard clamp test for insulin resistance showed that people with atrophy had about half the glucose uptake as healthy controls, while the HIV-infected control group had an intermediate level. More limb fat correlated positively with higher insulin sensitivity ($r = 0.60$, $P = 0.001$).

Several research teams strengthened this association in transgenic mice with virtually no subcutaneous fat. Besides severe insulin resistance, the mice have lofty triglycerides and hepatic steatosis. Transplanting fat from normal mice eases such metabolic abnormalities in one of these strains.

Can leptin reverse atrophy?

Another murine model—obese, hyperlipidemic, diabetes-prone Zucker rats—led Roger Unger (University of Texas Southwestern Medical Center, Dallas) to formulate the lipotoxicity hypothesis.¹⁰⁵ As circulating fatty acids begin roosting in nonadipose tissues, beta cells falter in secreting insulin, skeletal muscle become insulin resistant, and heart muscle weakens. Surveying six mouse or rat models, Schambelan listed disorders of fat regulation resulting from no adipocytes—or from too many adipocytes. “Adipocyte mass ranges from absent to massive,” he noted, “but the common feature of these disorders is lack of leptin action.”

A fat transplant from normal mice eased metabolic abnormalities in one of two mouse strains lacking subcutaneous fat. But leptin reversed metabolic abnormalities in both models. That finding has been extended to HIV-uninfected people with severe acquired lipodystrophy.¹⁰⁶ In one 17-year-old woman with no subcutaneous fat, leptin replacement brought levels back to the lower limit of normal, slashed stratospheric triglycerides, and controlled diabetes well enough to make antidiabetic drugs unnecessary. In eight people with severe non-HIV lipodystrophy, four months of leptin sharply reduced glucose and triglyceride levels.

Will leptin work in people with antiretroviral-induced lipodystrophy? Schambelan asked himself that question while evaluating 39 men referred primarily for fat accumulation, though most also had

fat atrophy. He found that 16 (41 percent) had leptin levels considered low in a National Institutes of Health trial—below 3 ng/mL. Levels in that nether range have proved more common in people referred primarily for atrophy.

Schambelan and colleagues have begun a trial in HIV-infected men with leptins below 3 ng/mL and women with levels below 4 ng/mL. Study participants must have fasting triglycerides between 299 and 1,000 mg/dL and clinical evidence of fat abnormalities. The protocol calls for 0.01 mg/kg of leptin for men and 0.02 mg/kg for women for three months. In the next three months the doses climb to 0.03 mg/kg for men and 0.06 mg/kg for women.



The IAPAC Sessions 2003 spanned a panoply of problems facing HIV clinicians. Even this two-day look at the challenges of HIV medicine suggests that clinicians must have more than a little facility in:

- Mental health
- Psychosocial issues
- Substance abuse
- Hepatology
- Adherence
- Pharmacology
- Pharmacokinetics
- Resistance
- Endocrinology
- Dyslipidemia
- Cell biology

No one can hope to excel in all those areas, but everyone must know what questions to ask and where answers might be found. As IAPAC Sessions Co-Chair Diane Havlir noted before the first talk, the best HIV clinicians are “the kind of people who know that the more you know, the more you don’t know.” And as each succeeding presentation made clear, anyone seeking a unifying theory of HIV disease had best seek retraining in a simpler discipline. Physics, maybe. These days an HIV paradigm, Havlir proposed, “is kind of an oxymoron.” ■

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Assessment of changes...

Continued from page 145

tion with the number of pills required per day. Nevertheless, no statistically significant differences were found regarding adherence, either in QD group evolution, or in the comparison between the QD and BID groups. Patients included in the study had both undetectable viral loads and demonstrated adequate adherence before switching to a QD regimen.

Undoubtedly, quality of life may benefit from a simplified treatment that results in fewer disruptions in the patient's life and it is more convenient for daily routines. Moreover, a simpler treatment increases the patient's satisfaction with therapy.

QD regimens have heretofore been offered to patients with a good virologic and immunologic status. Although patients who have been able to incorporate medication into their daily life as a habit will not necessarily show differences in adherence after switching from a BID to a QD regimen, it is imperative to develop studies to determine if these differences appear in historically adherent patients. For those patients who have marked difficulties in adapting a treatment to their daily lives because of, for example, complex job timetables or a hidden HIV condition, a QD regimen may represent a considerable improvement.

The impact of QD regimens in non-adherent patients also needs to be assessed. Nevertheless, it must be stressed that lack of adherence may sometimes be related to emotional conditions, such as the denial of illness or existence of symptoms of depression. Clinicians should attempt to ascertain the applicable cause of poor adherence in individual cases, offering alternative therapies and referring patients to appropriate specialists, as necessary.

Simplification strategies may facilitate the adaptation of a treatment to a patient's life but should always be offered in an individualized manner, considering the previous pharmacologic history, as well as the patient's preferences and lifestyle. Some patients will favor a simplified treatment but for others, a change in treatment may pose a source of stress (eg, new timetable, new drug names, fear of possible and unknown adverse events, or treatment failure). Thus, one of the basic pillars for successful treatment is to assure that the therapy chosen is the result of clinician and patient input and agreement. ■

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A B S T R A C T S

New England Journal of Medicine

Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia

Lazzarin A et al.

BACKGROUND: The T-20 vs Optimized Regimen Only Study 2 (TORO 2) compared the efficacy and safety of 24 weeks of treatment with the fusion inhibitor enfuvirtide in combination with an optimized background antiretroviral regimen with the efficacy and safety of the optimized background regimen alone. **METHODS:** The patients had previous treatment with each of the three classes of antiretroviral drugs, documented resistance to each class, or both and a plasma level of human immunodeficiency virus type 1 (HIV-1) RNA of at least 5,000 copies/mL. They were randomly assigned in a 2:1 ratio to receive either enfuvirtide (90 mg twice daily) plus a background regimen optimized with the aid of resistance testing (enfuvirtide group) or the background regimen alone (control group). **RESULTS:** Of the 512 patients who underwent randomization, 335 in the enfuvirtide group and 169 in the control group received at least one dose of study medication and had at least one follow-up measurement of plasma HIV-1 RNA. The median baseline plasma HIV-1 RNA level was 5.1 log₁₀ copies/mL in both groups. The median CD4 cell count was 98.0 cells/mm³ in the enfuvirtide group and 101.5 cells/mm³ in the control group. Patients had a median of seven years of previous treatment and had received a median of 12 antiretroviral drugs. The background regimen comprised a mean of four antiretroviral drugs in both groups. At 24 weeks, the least-squares mean change from baseline in the plasma viral load (intention-to-treat, last observation carried forward) was a decrease of 1.429 log₁₀ copies/mL in the enfuvirtide group and a decrease of 0.648 log₁₀ copies/mL in the control group, a difference of 0.781 log₁₀ copies/mL ($P < 0.001$). The mean increase in the CD4 cell count was greater in the enfuvirtide group (65.5 cells/mm³) than in the control group (38.0 cells/mm³, $P = 0.02$). **CONCLUSIONS:** The addition of enfuvirtide to an optimized background regimen provided significant viral suppression and immunologic benefit over a 24-week period in HIV-1-infected patients who had previously received multiple antiretroviral drugs.

N Engl J Med 2003 May 29;348(22):2186-95.

Alcoholism: Clinical and Experimental Research

Alcohol consumption and HIV disease progression: Are they related?

Samet JH et al.

BACKGROUND: The relationship between alcohol consumption and HIV disease progression has received limited attention in the era of highly active antiretroviral therapy (HAART). **METHODS:** We assessed CD4 cell count, HIV RNA levels, and alcohol consumption in the past month, defined as none, moderate, and at risk, in 349 HIV-infected people with a history of alcohol problems. We investigated the relationship between alcohol consumption and HIV disease markers CD4 cell count and HIV RNA level, stratified by HAART use, using multivariable regression. **RESULTS:** No significant differences in CD4 cell count or HIV RNA level were found across the categories of alcohol consumption for patients who were not receiving HAART. However, among patients who were receiving HAART, log HIV RNA levels were significantly higher in those with moderate (2.17 copies/ml) and at-risk (2.73 copies/ml) alcohol use compared with none (1.73 copies/ml; $p = 0.006$). CD4 cell counts in those with moderate (368 cells/microl) and at-risk (360 cells/microl) alcohol use were lower than for subjects who reported none (426 cells/microl; $p = 0.07$). **CONCLUSION:** Among patients who have a history of alcohol problems and are receiving antiretroviral treatment, alcohol consumption was associated with higher HIV RNA levels and lower CD4 counts. No comparable association was found for similar patients who were not receiving HAART. Addressing alcohol use in HIV-infected patients, especially those who are receiving HAART, may have a substantial impact on HIV disease progression.

Alcohol Clin Exp Res 2003 May;27(5):862-7.

Annals of Pharmacotherapy

Factors affecting patient adherence to highly active antiretroviral therapy

Escobar I et al.

OBJECTIVE: To determine the clinical and demographic variables related to adherence to highly active antiretroviral therapy (HAART) in patients treated in our hospital and identify the characteristics of nonadherent patients. **METHODS:** Outpatients receiving treatment with HAART ($n = 283$) were asked about variables related to adherence and to complete the APGAR (family support), State-Trait

Anxiety questionnaire (STAI) (emotional situation), and IAS (social support) questionnaires. Patients were classified in 2 groups depending on whether adherence was ≥ 95 percent or < 95 percent. Adherence was defined as the percentage of dosage forms prescribed that were obtained by the patient at the hospital pharmacy. A multivariate analysis was created to analyze how each significant variable affected adherence. **RESULTS:** Our data showed significant nonadherence for patients with the following factors: low level of education, unemployed, emotional situation, and abuse of substances including intravenous drugs. All significant variables were included in a logistic regression model to optimize the results. This model considered four variables: age (95 percent CI 0.89 to 0.99), number of antiretroviral drugs (95 percent CI 1.05 to 2.11), STAI Anxiety/Trait test (95% CI 2.02 to 6.02), and abuse of drugs (95 percent CI 1.20 to 3.95). **CONCLUSIONS:** We recommended special intervention to reinforce adherence for younger patients, patients taking a high number of antiretroviral drugs, those who have a history of intravenous drug use, and those with high anxiety status.

Ann Pharmacother 2003 Jun;37(6):775-81.

American Journal of Public Health

Use of alternative therapists among people in care for HIV in the United States

London AS et al.

OBJECTIVES: This study examined the influence of sociodemographic, clinical, and attitudinal variables on the use of alternative therapists by people in care for HIV. **METHODS:** Bivariate and multivariate analyses of baseline data from the nationally representative HIV Cost and Services Utilization Study were conducted. **RESULTS:** Overall, 15.4 percent had used an alternative therapist, and among users, 53.9 percent had fewer than five visits in the past six months. Use was higher for people who were gay/lesbian, had incomes above US\$40,000, lived in the Northeast and West, were depressed, and wanted more information about and more decision-making involvement in their care. Among users, number of visits was associated with age, education, sexual orientation, insurance status, and CD4 count. **CONCLUSIONS:** Among people receiving medical care for HIV, use of complementary care provided by alternative therapists is associated with several sociodemographic, clinical, and attitudinal variables. Evaluation of the coordination of provider-based alternative and standard medical care is needed.

Am J Public Health 2003 Jun;93(6):980-987.



I N T H E L I F E



Azeem H. Walele

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

This month, *IAPAC Monthly* is proud to feature Azeem Walele, who is Head of Pediatrics, Chief Specialist Pediatrician, and Head of Pediatric Infectious Diseases and HIV clinic at 2 Military Hospital, Wynberg, South Africa.

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

"Seek knowledge, from the cradle to the grave."

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

Hobbies: Collecting Swarovski crystal; Hidden talent: Motivating people.

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

South Africa, a gem opening up to the world.

Who are your mentors or real life heroes?

Nelson Mandela, a true statesman in the world.

With what historical figure do you most identify?

The Prophet Muhammed, his actions are still applicable today.

Who are your favorite composers and/or painters?

Composer: Johann Strauss; Painter: Leonardo DaVinci.

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

Birth of Islam.

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

Astrophysicist.

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

Greatest: Abolition of slavery (in some centers); Failure: Perpetuation of slavery (in some centers).

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

Poor, because of dreaded diseases, weapons of mass destruction, and ethnic cleansing. ■



[Strength in Numbers]

[IAPAC Welcomes New and Renewing Members]

In June 2003, the International Association of Physicians in AIDS Care (IAPAC) welcomed 29 new and renewing dues-paying members from five countries. IAPAC thanks the following physicians and allied health workers for their support of the association's mission to improve the quality of care provided to men, women, and children who are living with HIV/AIDS.

Nada Abou-Fayssal, *USA*
Gary Blick, *USA*
Jody Borgman, *USA*
Virginia Cafaro, *USA*
Kathleen Casey, *USA*
J. Wesley Cook, *USA*
Donald Cortum, *USA*

Jan Raffa Curtis, *USA*
Tory Dent, *USA*
Carol Encarnacion, *USA*
Joseph Eron, *USA*
Jim Farley, *USA*
W. Jeffrey Fessel, *USA*
Jerome Franz, *USA*
Catherine Hankins, *Switzerland*
Raymond Matta, *USA*
John Middleton, *USA*
Kathryn Mngadi, *South Africa*
Julio Montaner, *Canada*
Allison Nist, *USA*
Joseph Piperato, *USA*
Anne Pittman, *USA*
James Sosman, *USA*
Harold Stringer, *USA*
Alcides Troncoso, *Argentina*

Abdulla Ustadi, *United Arab Emirates*
Sonia Velazquez, *USA*
Fehmida Visnegarwala, *USA*
Daniel Wallace, *USA*

Also, the following are new and renewing institutional members: AIDS Community Services of Western NY, Inc.; Lifespan/Tufts/Brown Center for AIDS Research; and Mountain Reading Service.

To learn more about professional and institutional memberships, call (312) 795-4935 or send an e-mail to member@iapac.org. For more information regarding Corporate Partner opportunities, call (312) 795-4941 or send an e-mail to partner@iapac.org.

[Recruit your colleagues to join IAPAC]

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

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

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

Through the end of 2003, every new recruit who lists you as the member who referred him/her to IAPAC brings you

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

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

Shaping the future...

Continued from page 143

world's governments. The fight against HIV/AIDS as a whole relies on the work of informed and thoughtful advocates who bring attention to the pandemic and the threat it poses to humanity. IAPAC continues to host the International Conference on Healthcare Resource Allocation for HIV/AIDS because we are committed to facilitating new thinking and innovative solutions for equitable care and treatment. (This year's conference is scheduled to take place October 13-15, 2003 in Washington, DC.)

IAPAC is proud to have been one of the strongest and most consistent voices speaking on behalf of increased financial commitment to global AIDS. Now that preliminary signs of initiative have been put forth by select countries, it is imperative that IAPAC take a strong stance in encouraging other governments to make sure that preventing and treating HIV disease is at the center of sound domestic and international policy. Key among the messages that we intend to continue stressing is the need for adequate support of the Global Fund to Fight AIDS, Tuberculosis, and Malaria.

As in all areas of IAPAC's work, we hope and anticipate that our advocacy will draw on an increased membership and new permanent regional offices to serve them. With a global membership of 12,000-plus in 99 countries as of June 2003, we have a formidable force to marshal in this struggle and we want to continue to take our strength and direction from physicians and allied healthcare professionals devoted to improving the care and treatment of all men, women, and children living with HIV/AIDS. As we undertake to demonstrate to governments, funding institutions, and partner organizations the priorities for enhanced HIV care and treatment that those at the front lines of the battle against HIV/AIDS feel are required, we will continue to count on the support and input of our global membership.

The future is uncertain in the midst of the pandemic, but with a force such as this, fully motivated and working together, we can do a great deal to shape it. ■

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

6th International Conference on Healthcare Resource Allocation for HIV/AIDS

Healthcare Systems in Transition

October 13-15, 2003

Westin Embassy Row - Washington, DC

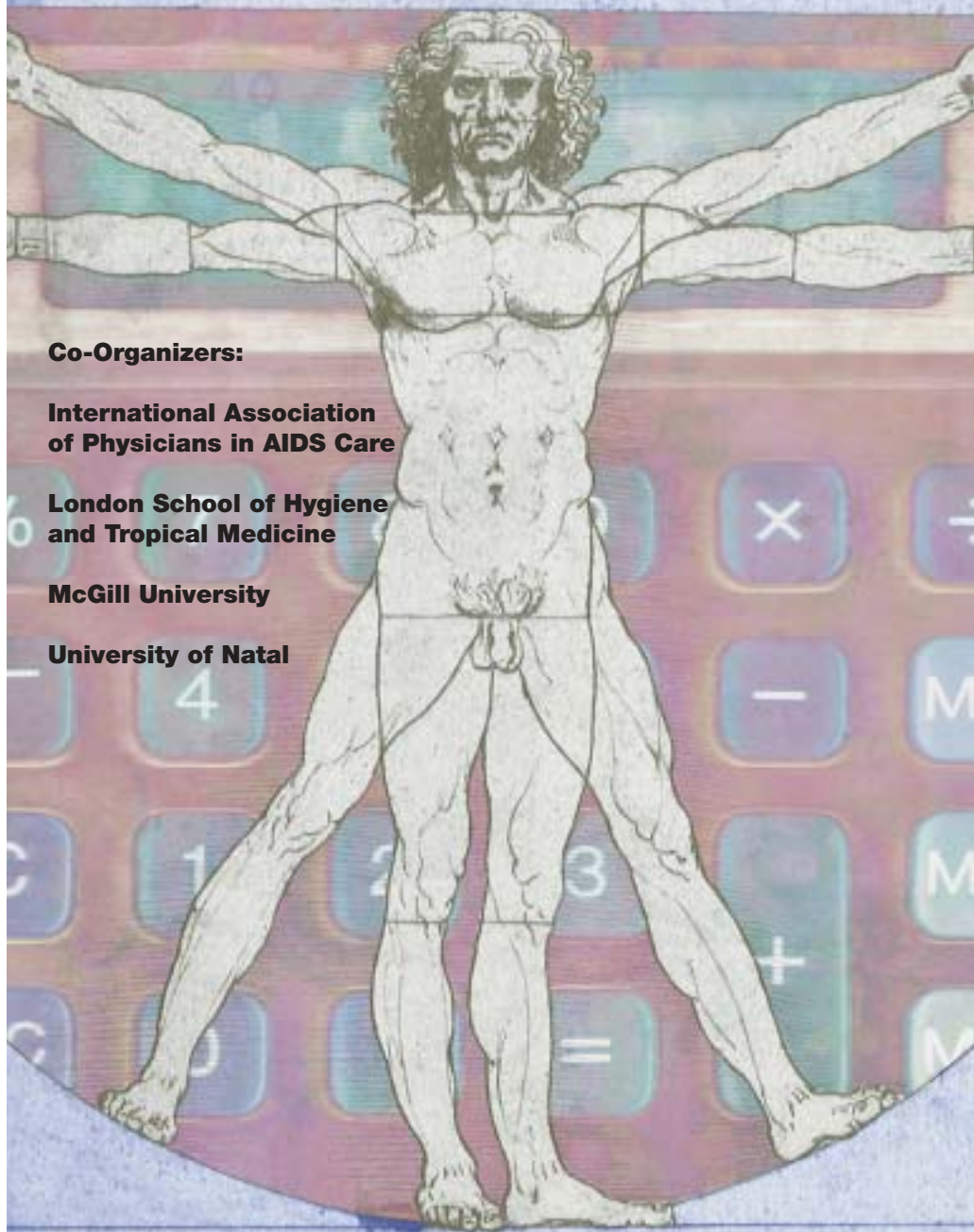
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To learn more, visit www.iapac.org.



SAY ANYTHING



US President George W. Bush signs the United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria Act of 2003 during a May 27, 2003, signing ceremony held at the US Department of State in Washington, DC.

White House photo by Tina Hager.

Editor's Note: This edition of Say Anything is devoted to responses to the US Emergency Plan for AIDS Relief, which President George W. Bush signed into law on May 27, 2003. Alternately referred to as the United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria Act of 2003, the legislation approves up to US\$15 billion over five years for care, treatment, and prevention efforts in 14 African and two Caribbean countries, and allows support for the Global Fund to Fight AIDS, Tuberculosis, and Malaria of up to US\$1 billion per year, with the provision that US funding may not exceed more than one-third of the total.

With today's bill signing, the world moves an important step closer to supporting a response that begins to match the magnitude of the challenge. But there is still a long way to go. Peter Piot, Executive Director of UNAIDS, in a May 27, 2003, Reuters report.

Other wealthy nations of the world—specifically G-8 member nations—must follow suit with similar funding increases.

IAPAC President/CEO José M. Zuniga in a May 27, 2003, Associated Press report published prior to his attending the signing ceremony in Washington, DC.

There is no question that this represents a whole new day [for US efforts against AIDS]. But we have to hold everyone's feet to the fire, including Congress and the president, in getting the dollars.

Mark Isaac, Vice President of the Elizabeth Glaser Pediatric AIDS Foundation, in a May 27, 2003, Reuters Health report.

All [US]\$3 billion is urgently needed. We're talking about real numbers, but not the numbers that can win this battle.

Jeffrey Sachs, Special Advisor to United Nations Secretary-General Kofi Annan, as quoted in a May 28, 2003, Philadelphia Inquirer article.

You'll think I'm off my trolley when I say this, but the Bush administration is the most radical—in a positive sense—in the approach to Africa since Kennedy.

British Live Aid founder and rock musician Bob Geldof speaking to The Guardian in a May 28, 2003, article.

The devil is really in the details. Between the tax cuts and all the money being spent on terrorism, there's little discretionary money left. It will be extremely difficult [to actually supply the approved funding].

Fred Dillon, Policy Director for the San Francisco-based Pangea Global AIDS Foundation, in a May 28, 2003, San Francisco Chronicle article.