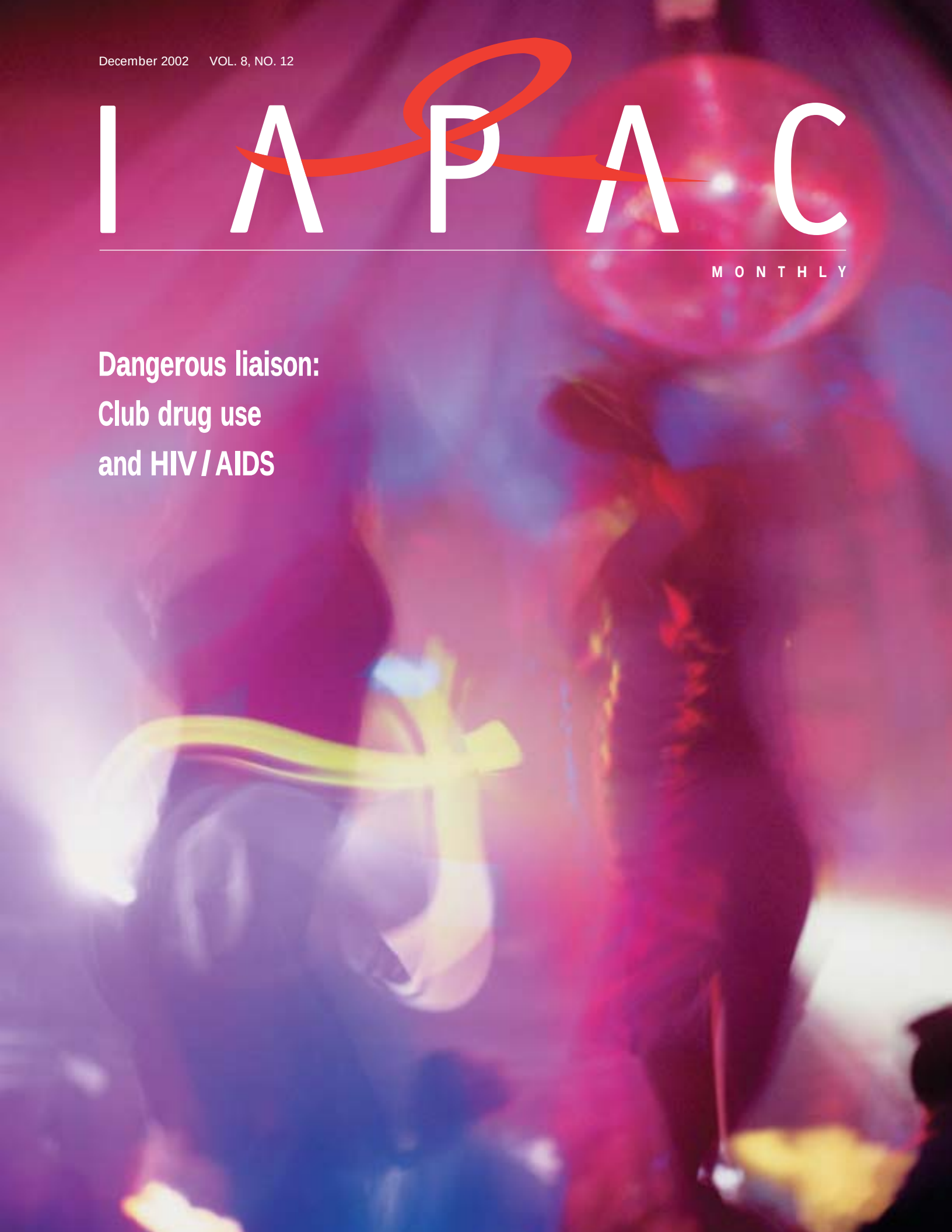
December 2002 VOL. 8, NO. 12

IAPAC

MONTHLY



Dangerous liaison: Club drug use and HIV / AIDS

December 2002

IAPAC MONTHLY

Volume 8, Number 12

DEPARTMENTS

IAPAC

battling complacency
advancing commitment

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

PRESIDENT/CEO José M. Zuniga

CONTROLLER Harry J. Snyder

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

EXECUTIVE DIRECTOR Mulamba Diese

DEPUTY DIRECTOR Tania Adendorff

IAPAC MONTHLY

EDITOR-IN-CHIEF José M. Zuniga

MANAGING EDITOR Lisa McKamy

POLITICAL EDITOR Scott A. Wolfe

CREATIVE/DESIGN DIRECTOR Holly J. Emanuelson

ADVERTISING DIRECTOR Michael S. Glass

WRITER-AT-LARGE Mark Mascolini

CONTRIBUTING WRITERS Lisa Keen, Dave MacDougall

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

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

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

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

Looking to 2003

José M. Zuniga

As I write this 36th consecutive Report from the President, 2002 is nearly at its end. Thus, this is a particularly important time for reflection, introspection, and planning for what lies ahead. Looking both within the United States and abroad, I am filled simultaneously with emotions of frustration and hope for what has and has not been accomplished this past year in the global battle against HIV/AIDS. I expect that I share many of these emotions with the members and partners of the International Association of Physicians in AIDS Care (IAPAC) who look to the association for leadership on advocacy, education, and capacity-building issues aimed at ensuring effective care for all people living with and affected by HIV/AIDS. I am humbled by the images of millions worldwide who have perished this year as a result of AIDS, where so many others have benefited from access to effective antiretroviral therapy. The global inequities that inform this difference reveal the worst in the human character.

In view of the mixed plate of frustrations and hopes that is our current diet, I choose to speak to the accomplishments IAPAC achieved this year, and our commitments for 2003. I do so less in immediate praise of IAPAC's accomplishments than as a continued plea for your support and your collective commitment to responsibility as arbiters of health and human dignity. Further, I present to you the following description of IAPAC's 2002 activities and plans for 2003 in order to urge you to hold IAPAC and others to the tasks that must be fulfilled in redressing the AIDS pandemic.

The year 2002 was a year of tremendous growth for IAPAC. As many long-standing

observers and members of the association will testify, IAPAC has transformed from an almost exclusively US-based and -guided association to one that is now truly reflective of the global reach and diversity that our name suggests. In this respect, the association welcomed additional international clinical and policy leaders to the IAPAC Board of Trustees, as well as to the roster of staff that fulfills the association's mandate. There is "Strength in Numbers," as IAPAC's ongoing membership slogan suggests, but also strength in diversity and representation, as our leadership and staff structures reveal.

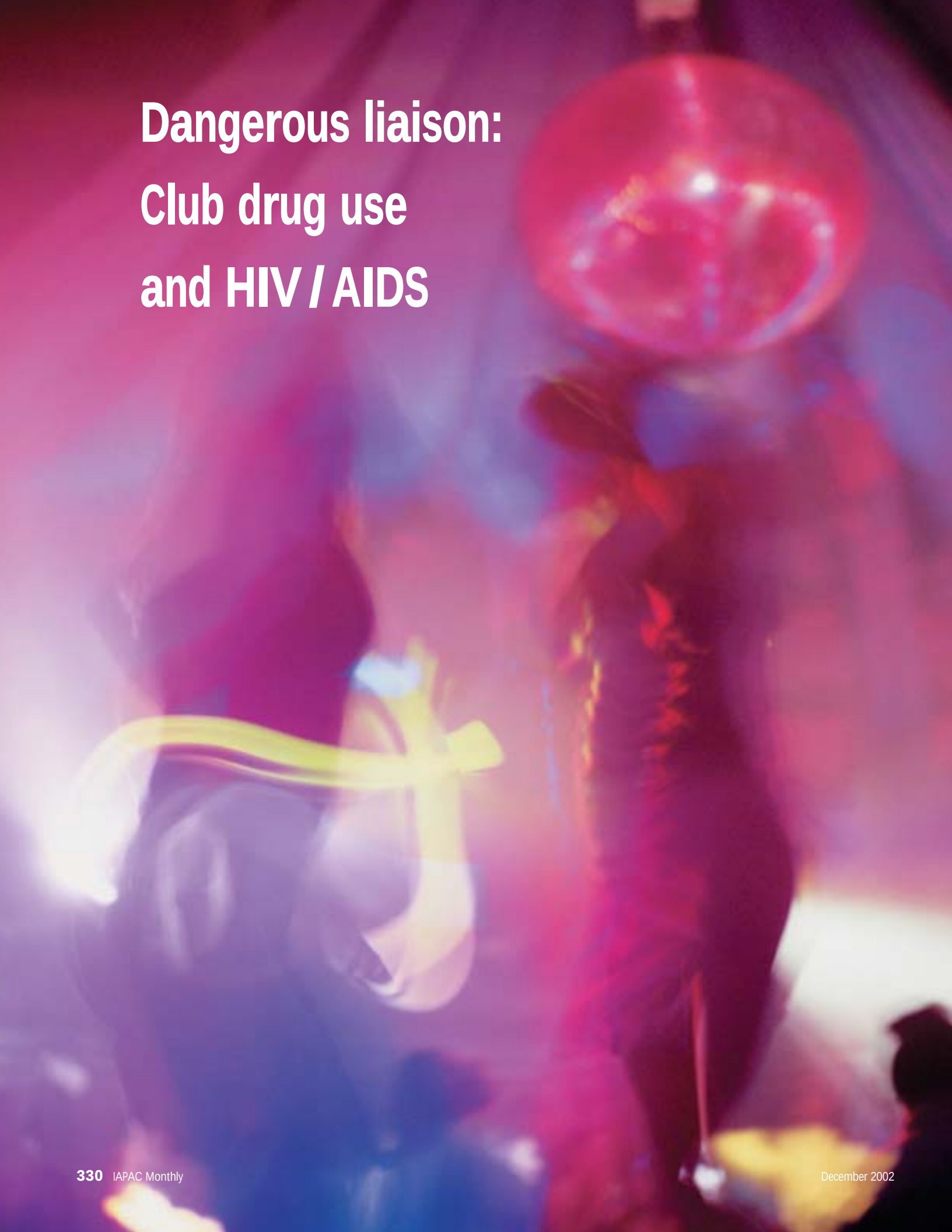
The association also grew significantly in its programmatic reach and depth, across each of its three main areas of activity. With respect to IAPAC's critical advocacy role to increase the quality of and access to care and treatment for those living with HIV/AIDS, our revised Web site was launched in July 2002, with expanded physician, patient, and allied healthcare professional member services and information. We anticipate the Web site to be fully developed by early 2003, thus providing the necessary means to express regular policy and clinical statements on pressing international care and treatment issues, in addition to those frequently distributed to media and partners. Also critical in terms of IAPAC's role as advocate were continued support for and recognition of key HIV care providers and patient-advocates through the annual Honoring Our Heroes awards event, this year held October 26, 2002, in Chicago, and participation in key policy and clinical symposia and conferences such as the XIV International AIDS Conference in Barcelona.

Medical education continued to assume the largest portion of IAPAC staff time, building upon momentum and promises made in 2001. For example, IAPAC distributed more than 50,000 IAPAC Drug Guides, featuring monographs of the 19 US Food and Drug Administration (FDA)-approved antiretroviral agents. IAPAC also produced and distributed 30,000 sets of GRIP Guides—user-friendly physician/patient interaction guides visually articulating US Department of Health and Human Services (DHHS)-recommended antiretroviral regimens. These reference tools are meant to ensure appropriate HIV treatment and patient adherence to prescribed drug regimens.

IAPAC also continued publication and global distribution of our member magazine, *IAPAC Monthly*, and launched in early 2002 a new quarterly, peer-reviewed clinical journal entitled *JIAPAC*. Adding to quarterly *JIAPAC* issues in 2002 were regular

Continued on page 340

Dangerous liaison: Club drug use and HIV / AIDS



Jan Swanson and Alan Cooper

Club drugs, or recreational drugs, as they are sometimes called, have only recently been associated with increased high-risk sexual behaviors which, in turn, may cause higher incidence of HIV/AIDS. By club drugs, we mean a number of illegal, mostly synthetic drugs that are commonly used in nightclubs, "raves," and circuit parties.[1] In this article, we will be referring to club drugs and recreational drugs interchangeably.

Injection drug use has been known almost since the outbreak of the epidemic to be a means of spreading the virus by way of contaminated blood. In recent years, it has become increasingly clear that injection drug users (IDUs) are not only at increased risk of HIV infection from infected needles and shared drug paraphernalia but also as a result of high-risk sexual behaviors. The latter include trading sex for money and unprotected sex fueled by high sex drive associated with cocaine and amphetamine use.[2]

Even among short-term young IDUs, sexual practices, and not just injecting practices, were found to be important predictors of HIV infections.[3] Gay and bisexual men who inject drugs appear to be at greatest risk, as indicated, for example, by their HIV seroprevalence increasing in San Francisco from 25 percent in 1996 to 42 percent in 2000, while heterosexual male IDUs remained at a stable rate.[4]

A study by Strathdee et al followed 1,800 IDUs for 10 years in Baltimore and found that high-risk sexual behavior was a better predictor of HIV infection than was sharing needles while injecting drugs. They found a gender difference in the type of sexual activity that predicted greatest risk, however. Among men, high-risk homosexual activity was the best predictor. Among women, high-risk heterosexual activity was the most important factor.[5]

Club drug users, not wanting the stigma or risks of injection drug use, prefer drugs such as MDMA (Ecstasy), ingested in pill form. This allows users to avoid track marks, and other signs of hard drug use and contribute to a belief that taking club drugs is harmless as well as fun.[6]

Particularly in the gay/bisexual community, drugs such as MDMA have become increasingly popular within a significant drug-using subset. A large probability telephone sample of urban men who have sex with men (MSMs) taken at four large American cities found a 52 percent prevalence of recreational drug use.[7] A separate study in New York City found that 13.7 percent of a sample of MSMs reported using MDMA within the past six months, using it an average of 6.24 times in that period. Compared with non-users, MDMA users were found to have more male partners, have more one-night stands with men, and have more unprotected anal sex with men.[8] There was clearly an association between club drug use and high-risk sexual behaviors.

This article will examine club drugs, their effects and risks, as well as some of the settings in which they are used. We will also look at the relationship between drug use, sexual behavior, and risk for HIV/AIDS. We will discuss how recreational drugs may interact with highly active antiretroviral therapy (HAART). We will also look at some of the efforts that have been made in prevention and harm reduction strategies to reduce the transmission of HIV. Finally, we will discuss the role of the physician or allied health professional in assessing and treating the drug abusing or dependent patient with or at risk for HIV/AIDS.

Raves and circuit parties

Raves have become increasingly popular since the 1980s. They are nighttime dance parties originally held in large, abandoned warehouses or in farm fields and more recently in legal spaces such as concert halls and underground parking lots.[9] Attendance has been as high as 20,000 participants. Raves attract primarily middle-class heterosexual 15- to 25-year-olds who hear about them on the Internet or by word of mouth. They can involve up to two days of dancing, lights, and electronic music, often presided over by a popular DJ. Raves are characterized by consumption of club drugs in "cafeteria" fashion, in which whatever drugs are available are often sampled. The pills often contain adulterants which may be more toxic than the club drug itself. Also, as drugs are combined during the same event, undesirable and unpredictable effects can result.[10,11]

Circuit parties have also grown in popularity and are common throughout the world. They are large-scale dance events that last for several days and tend to occur each year at about the same time in a particular city. These annual events are so named because they appear to follow a circuit from one city to another every few weeks.[12]

Unlike raves, circuit parties are attended primarily by gay and bisexual men who come to participate in late-night dance events, as well as in multi-event entertainment such as popular singers, all male revues, and frequently homoerotic events. Large parties can attract 20,000 men to a particular community. This is typically a somewhat older crowd than those attending raves, often upper-middle-class white men in their 30s.[12,13]

More than 80 percent reported drug use during these events, according to one recent study.[14] According to the Circuit Party Men's Health Survey of the San Francisco Bay Area,[13] 78 percent of the participants were between 25 and 39, attended a median of three parties in the previous year, and a significant number (25 percent) reported at least one incident of drug overuse during that same time. Most of the men had taken MDMA or ketamine, as well as other popular substances, during the most recent circuit party weekend. While nearly all participants were motivated by the desire "to listen to music and dance," and "to be with friends," a majority of men endorsed "getting high on drugs" as a motivation, whereas nearly a third were there to "have sex." When the authors compared three-day drug use rates with six-month rates from a general population sample of gay men,[7] men reported much lower use of amphetamines, cocaine, and Ecstasy during the six-month time period. Mansergh et al conclude that a "substantial drug culture permeates the circuit party environment."

Some organizations that provide case management, medications, and other services to persons with HIV/AIDS, such as AIDS Arms, Inc., in Dallas, have refused to be a recipient of funds from these events (circuit parties) because of the illicit drug use "that dramatically impair[s] an individual's judgment increasing the likelihood of engaging in unsafe sexual practices."[15]

Club drugs

The US National Institute of Drug Abuse (NIDA) describes *club drugs* as a vague term that refers to a wide variety of drugs that grew in popularity along with dance club culture in the 1990s. Older party drugs such as cocaine, popular in the 1980s, are not as widely used since their health risks have become more widely known. Drugs that have become increasingly abused include methamphetamines,

3,4-methylenedioxymethamphetamine (MDMA), gamma-hydroxybutyrate (GHB), flunitrazepam (Rohypnol), and ketamine. Each can cause serious health problems, and even death, in spite of a popular misconception that taking them is a safe way to enhance the dance party experience.[6] In the United States, 9.1 percent of college students and 7.2 percent of young adults (ages 19-28) reported in 2000 that they used MDMA at least once in the last year.[16] Similarly, a study of over 3,000 university students in the United Kingdom reported that 13 percent had used MDMA.[17] Winstock et al reference reports of use and related problems in Denmark, Germany, Spain, Australia, and the Netherlands.[18]

3,4-Methylenedioxymethamphetamine (MDMA)

Street Names: Ecstasy, X, E, Adam, Hug Drug

Ecstasy is an amphetamine with both stimulant and hallucinogenic properties. It is usually taken orally as a tablet or capsule. It is used to reduce inhibitions and create feelings of empathy for others as well as deep relaxation. The stimulant effect allows the user to stay up all night, as its effects last four to six hours. With repeated use, the user may stay up for two- to three-day parties.[1,19] It can produce significant increases in heart rate, myocardial oxygen consumption, and blood pressure, which is particularly risky for persons with circulatory or heart disease.

MDMA, along with other popular substances, such as alcohol, is used for extended dancing in hot and crowded conditions. These factors increase its toxicity and lead to dehydration, hyperthermia, seizures, kidney and cardiovascular system failure, and may lead to death.[20,21]

Regular use causes lasting damage to neurons that release serotonin, changes that have been shown to persist for many years in animals, and may cause memory impairments, disrupted sleep, depression, and anxiety. Studies in Great Britain and Germany found that MDMA users, even after six months of non-use, performed more poorly on some memory and learning tests than non-users.[20]

A case study of club drug using MSMs in Boston and New York found that more than 50 percent of the men in the study combined MDMA with other drugs such as ketamine, cocaine, methamphetamines, and Viagra.[22]

Gamma-hydroxybutyrate (GHB)

Street Names: Liquid Ecstasy, Grievous Bodily Harm, G, Georgia Home Boy, Fantasy.

GHB is a central nervous system depressant banned by the US Food and Drug Administration (FDA). It generates feelings of euphoria, sedation, and well-being, and can also be used to counteract over-stimulation by MDMA. It is available in clear liquid or a white powder that can be added to water and mixed with flavorings. It may also be sold as a capsule or tablet.[19]

Adverse effects include its ability to slow down breathing and heart rate to dangerous levels. At lower dosages, it causes sedation, nausea, and visual changes. Overdose may occur rather quickly, and can lead to seizures, hypothermia, loss of consciousness, coma, and ultimately death. In 1999, there were 2,960 medical emergencies related to GHB use in the United States compared to 790 in 1998.[23] As of January 2000, the US Drug Enforcement Agency (DEA) reported 60 GHB-related deaths.[1]

GHB has also been implicated in sexual assaults and is considered a "date rape" drug. It can cause the victims to be incapable of resisting rape and to have difficulty remembering the details of the assault at a later time, rendering them unreliable witnesses.[1] It has been incorrectly perceived as a safe drug because, until recently, it was available in health food stores as a supplement.[23]

Ketamine

Street Names: K, Special K, Vitamin K, Cat Valium, Horse Tranquilizer

Ketamine is marketed as a short-acting general anesthetic for human and veterinary use. As a liquid or powder, it can be injected, added to smokable materials, or consumed in drinks. It produces dream-like or hallucinatory effects.[19,24] Low doses produce a mellow, colorful experience whereas higher doses can create "out of body" or "near death" experience, loss of consciousness, delirium, amnesia, seizures, and even, in some cases, fatal respiratory events.[1,25]

When combined with alcohol, the greatest risk is falling asleep or collapsing, and then vomiting and possibly choking on one's own emesis.[26]

Flunitrazepam (Rohypnol)

Street Names: Roofies, Roche, Forget-me pill, Mexican Valium, Rope, Ropies, Roaches

Rohypnol is a benzodiazepine illegal in the United States but available in many countries as a sedative or presurgery anesthetic. It can be taken orally in tablets or dissolved in drinks even without the person's knowledge, since it is tasteless and odorless.

It is known as a date rape drug because it can render its victim helpless and unable to remember clearly what took place. It can also lower blood pressure and cause drowsiness, dizziness, confusion, and visual disturbances.[1,19]

Methamphetamine

Street Names: Speed, Ice, Crank, Meth, Fire, Glass, Crystal

Methamphetamine is a very addictive stimulant. It is a white powder that can be snorted, smoked, injected, or taken by mouth. It has become an alternative to MDMA at some clubs and raves although it is not as popular as other synthetic drugs at these settings. Like MDMA, it is used for high levels of energy needed in raves, clubs, and circuit parties, as well as for feelings of euphoria, increased self-confidence, and hypersexuality.[1,27]

Abuse can result in damage to the central nervous and cardiovascular systems, irritability, hypothermia, aggressiveness, paranoia, and anxiety, as well as strokes, myocardial infarctions, and permanent damage to the blood vessels. Long-term use has been linked to an induced paranoid psychosis associated with delusions of persecution and hallucinations.[27]

In the major metropolitan areas of the western United States and their gay communities, it seems to be reaching epidemic levels of abuse.[28] It also appears to be on the rise among sexually active gay men in New York City.[27]

d-Lysergic Acid Diethylamide (LSD)

Street Names: Acid, Yellow Submarines, Cubes, Trips

This powerful hallucinogen is easily available at concerts and raves. Its potency varies from 20 to 80 micrograms per dosage unit, much less than the 100 to 300 microgram dosages common in the 1960s. It is now distributed in thin squares of gelatin, treated sugar cubes, or applied to blotter paper. At today's lowered potency, fewer emergency room visits occur, accounting for some of its continuing popularity.[1]

LSD produces distortions in sensory perceptions and rapid mood swings, ranging from intense fear to euphoria.[25]

Typically, the effects of the drug include higher body temperatures, increased heart rate and blood pressure, sweating, sleeplessness, and tremors. Long-term effects include persisting perception disorders known as "flashbacks."[19]

Sildenafil (Viagra)

Viagra is being combined with such club drugs as MDMA to enhance sexual experience. In a study in a sexually transmitted disease clinic in San Francisco, 32 percent of gay respondents and 7 percent of heterosexual male respondents reported using Viagra.

Combinations such as amyl nitrite (poppers) and Viagra can result in priapism, myocardial infarctions, and stroke. Gay men who use Viagra report more sexual partners and more risky sex (partners who are HIV-positive or are of unknown HIV status) than straight men.[29]

A study of more than 2,000 night club customers in the United Kingdom found 3 percent who reported using Viagra recreationally, usually simultaneously with illegal drugs such as cocaine, methamphetamines, or cannabis. They reported feeling enhanced sexual desire and "warmth." Less than half reported negative effects such as headaches and genital soreness.[30]

Drug use, sex, and the risk of HIV

The relationship between drug use and unsafe sexual practices among gay men has been shown in many studies.[27,31-33] These unsafe sexual practices put gay and bisexual men at greater risk for HIV infection. Gay and bisexual men who do not use drugs report fewer acts of insertive and/or receptive anal intercourse without condoms than do recreational drug-using gay and bisexual men.[34]

Methamphetamine shows documented prevalence rates ranging between 5 percent and 25 percent of the gay and bisexual men studied across many cities from Honolulu to Denver.[27] It is used to increase sensory experiences, especially sexual ones, and to create feelings of euphoria, which may contribute to increased sexual risk-taking. It has been associated with infrequent use of condoms, perhaps as a result of the above factors.[35]

Methamphetamines can also increase risk for HIV/AIDS by increasing sexual sensation at the same time that it may interfere with erections, colloquially referred to as "crystal dick." A result of this problem can create "instant bottoms," a term applied by gay and bisexual men to drug users who take on the receptive role during anal intercourse. This practice is the riskiest sexual behavior that may cause HIV infection,[36] particularly when condoms are not used. Gay and bisexual men who use amphetamines have 2.9 times greater risk of HIV infection through receptive anal intercourse than men who do not use the drug.[27] Use of any stimulant drug, not just methamphetamines, has been associated with unprotected anal intercourse.[37]

MDMA was reported to be in wide use among gay and bisexual men recruited from three dance clubs in New York City,[14] and was found to be the only recreational drug associated with unsafe sex in this sample. Other drugs have been related to high-risk sexual behavior in different studies.[32, 38-40]

Circuit party weekends have also been associated with high-risk sexual behavior. A study by Mansergh et al reported that 29 percent of their sample of gay and bisexual men had multiple sex partners during a single circuit party weekend. Of this higher-risk group, 47 percent reported unprotected anal sex. They concluded that sexual activity, including unprotected anal sex, was relatively common during these weekends.[13]

Colfax and his associates studied 295 gay/bisexual men in San Francisco and measured drug use and sexual risk-taking during a San Francisco circuit party (CP), a circuit party held in another geographical area (distant CP), and non-CP party weekends. They found a high use of drugs during CPs. For example, at a distant CP, 80 percent used MDMA, 66 percent used ketamine, and 43 percent used crystal methamphetamines. Drug use during CP weekends was greater than during non-CP weekends.

Unprotected anal sex with partners of unknown or opposite HIV serostatus was most prevalent during distant CP weekends, perhaps because the gay/bisexual men felt less inhibited away from their own city and took more sexual risks. The strongest predictors of unprotected anal sex with opposite or unknown serostatus partners were being HIV-positive and use of crystal methamphetamines, Viagra, or amyl nitrites. The authors conclude that the level of high-risk activity during circuit parties suggests significant potential for HIV transmission.[41]

In another study on circuit parties, Mattison et al found that use of amyl nitrites (poppers), MDMA, ketamine, crystal methamphetamines, and GHB were associated with unsafe sex. In a large nonrandom sample of party attendees, more than 50 percent reported using alcohol, MDMA, and ketamine. Frequent use of MDMA, ketamine, and poppers had a significant association with unsafe sex at parties. Crystal methamphetamines and GHB only showed a trend although in the expected direction.[42]

Chesney et al suggest that seroconversion may be mediated by these drug-related factors:

1. Stimulants and inhalants increasing arousal and delaying ejaculation.
2. Disinhibition effects of drugs.
3. Substance abuse and high-risk sexual behaviors occurring within social networks if unprotected anal intercourse is a norm in such networks and there is a high-risk background prevalence of HIV.[43]

Club drugs, in particular MDMA, methamphetamines, and poppers, encourage risky sexual practices, at least among gay/bisexual men, such as multiple sexual partners and unprotected anal or receptive anal intercourse, and thus increase the risk of HIV/AIDS. Circuit parties, especially distant circuit parties, encourage high-risk sexual behaviors and club drug use among gay and bisexual men. We are not aware of studies focusing on raves with a primarily heterosexual population and increased risk for HIV/AIDS.

The effects of club drugs on HAART and adherence to HAART

Club drugs can affect HAART both through drug interactions and by affecting adherence to HIV drugs. Interestingly, although alcohol interacts with many club drugs, alcohol appears to have the least interactions with protease inhibitors and nonnucleoside reverse transcriptase inhibitors. Methamphetamines and MDMA have a potential interaction with all of the protease inhibitors and delavirdine. GHB has a potential interaction with ritonavir. Marijuana has a potential interaction with lopinavir and rivonavir.[44]

MDMA is demethylated by CYP2D6, an isozyme. The protease inhibitor ritonavir is a potential inhibitor of CYP2D6. Thus, taking MDMA with ritonavir could theoretically lead to toxic effects due to a high plasma concentration of MDMA. This may be caused by this inhibition of demethylenation, the principle pathway by which MDMA is metabolized.[45]

Henry and Hill describe a fatal interaction between ritonavir and MDMA in a man who had been HIV positive since 1991 and developed AIDS in 1995. In September, 1996, his regimen of zidovudine 200 mg three times a day and lamivudine 150 mg twice a day was altered to include 600 mg of ritonavir twice a day. He had taken MDMA on several occasions without problems on his prior medication regimen. He went to a club on October 6, 1996 and swallowed three tablets of MDMA. He drank beer and four hours after his arrival, he became seriously ill and died. A nurse who was attending the club described him as hypertonic, sweating, breathing rapidly, tachycardic, and cyanosed. The subject told the nurse that he had taken about 180 mg of Ecstasy. He then had a tonic-clonic convulsion. A few minutes later he vomited and had a cardiorespiratory arrest and could not be resuscitated. An autopsy was done. His lungs were edematous and congested. It was felt that the gentleman died from a severe serotoninergic reaction to Ecstasy. It is hypothesized that the ritonavir increased the level of the Ecstasy to a toxic level. The authors believe that ritonavir could react with many drugs metabolized by CYP2D6, including amphetamine derivatives, and people who use party drugs should be advised of this interaction.[45] Other researchers have noted that the effect of methamphetamines has been demonstrated to be two to three times greater for individuals on combination therapy, especially combinations including ritonavir.[46]

Protease inhibitors are metabolized primarily by the hepatic cytochrome P450 system (isozyme CYP3A4) and also inhibit and induce this enzyme in varying degrees. Ritonavir also affects three other P450 cytochrome enzymes, CYP2D6, CYP2C9, and CYP2C19.[47] Three party drugs—amphetamine, MDMA, and methamphetamine—are metabolized by the CYP2D6 isoform of the cytochrome P450 system. Ritonavir can increase levels of these party drugs. Interestingly, ritonavir, by induction of the CYP3A4-mediated metabolism and glucuronidation of several drugs, decreased drug levels of methadone, alprazolam and meperidine hydrochloride, which are metabolized by CYP3A4. This has caused a withdrawal syndrome with these drugs.

Other drugs whose metabolic pathways are altered by protease inhibitors are benzodiazepines, opiates, marijuana, zolpidem, and Viagra. These drugs are not infrequently used with recreational drugs. The question that arises is what happens when many drugs are used together that are metabolized by the same metabolic pathway. Harrington and colleagues in Seattle believe that HIV providers should caution their patients that drug interactions between recreational drugs and medications are complex, unpredictable, and even dangerous. Some interactions are known and some are not, making this an even more serious situation.[47]

Khalsa et al believe that directions for future research should include studying the underlying mechanisms of drug interactions and metabolic pathways, interactions between illicit drugs, licit drugs, and prescription drugs. They recommend developing educational programs for clinicians to understand and treat drug interactions among drug users.[48]

Adherence

Halikitis and colleagues presented an abstract at the XIV International AIDS Conference on adherence to HIV medications and club drug use among gay and bisexual men. The researchers sampled 300 gay/bisexual men; 51.9 percent missed one dose of their medicines in the two-month period prior to assessment and 47.5 percent missed one dose in the last two weeks. Based on the Abuse Screening Test, substance users/abusers reported more doses missed than non-drug users. Individuals who used club drugs were less adherent than those reporting no substance use and less adherent than those individuals who abused drugs other than club drugs. The researchers concluded that club drug use impacted adherence to HAART and needs to be addressed. They believe that this lack of adherence could be a result of the disinhibitions caused by the use of club drugs, as well as the contexts in which the substances are used.[49]

This is an important observation, as other researchers have found a similar association between alcohol and drugs and adherence to HAART. Lucas et al in a study of 764 HIV-1 infected patients found that active drug users were more likely to report nonadherence to medication and to have smaller median reductions in HIV-1 RNA from baseline and smaller median increases in CD4 counts from baseline than patients who were non-users and former drug users.[50]

The data regarding adherence problems to HAART medication and alcohol and recreational drugs are not always consistent. For example, Sauders et al studied 78 subjects with varying use of alcohol and recreational drugs (heavy users, moderate users, non-users). In this small sample they found no relationship between alcohol and recreational drug use and adherence problems. The heavy users had reported few problems with adherence but this may have been due to motivation to exaggerate actual compliance.[51]

Current research suggests that alcohol and drug use may affect adherence to HAART and possibly affect T cell counts and viral loads. The reasons for these effects are unclear. The reasons may relate to psychological and social problems stemming from drug use. Club drug users may have higher nonadherence rates possibly due to disinhibition of behavior caused by the recreational drugs.

Recreational drugs may also interact with antiretrovirals and with other substances, such as alcohol, Viagra, opiates, and marijuana, possibly creating a potentially dangerous and life-threatening drug combination. Club drugs may affect adherence to HAART and may have serious drug interactions with antivirals, such as ritonavir. Further study on this important topic is required.

Prevention and harm reduction

What is the difference between prevention and harm reduction?

Prevention programs aim to lower the rate of onset of particular disorders, such as illicit drug use in a community, by intervening when potentially harmful conditions exist.[52] Examples of prevention programs are programs that encourage individuals not to attend raves or circuit parties to prevent exposure to the considerable drug use in these settings, programs that encourage saying no to drugs, and programs that encourage individuals not to start smoking. Harm reduction approaches, in contrast, attempt to prevent the potential harmful effects of drug use rather than preventing the drug use itself.[53] They are, however, compatible with prevention approaches and are in no way opposed to them. Examples of harm reduction programs are needle exchange programs and methadone maintenance.

Harm reduction is the opposite of prohibition. For instance, Great Britain responded to the health risks posed by raves by attempting to prohibit them. Rave organizers faced heavy fines and imprisonment. These measures failed because the parties moved to legitimate clubs where the dancers mixed alcohol with drugs, thereby increasing the health risks. Prior to the law, enacted by the British government prohibiting raves, only 9 percent of respondents in the 16- to 29-year-old range used Ecstasy. This rose to 91 percent among members of the dance club scene.[9] A harm reduction approach, by contrast, could try to ensure that buildings met safety and health standards and had adequate security, and that education about health effects of the drugs was available from trained volunteers. This approach has been adopted by leaders of the rave community and by various health departments.[9]

Prevention programs are often based on the results of studies focused on the targeted communities. At other times, the prevention programs stem from members in the affected communities developing community-based programs. The following ideas come from both research and community organizations. Colfax et al recommended the following strategies of prevention based on their research on drug use and sexual risk behavior among 295 gay/bisexual men from the San Francisco Bay area.[41]

1. Because one third of HIV-positive men in their study used Viagra and its use was associated with unsafe sexual practices, they suggested that physicians should reinforce safer sex messages before prescribing Viagra, and that HIV prevention programs should address potential recreational Viagra use.
2. Colfax and colleagues found that men who participated in distant city circuit parties engaged in more high-risk behaviors. The researchers believed that these men were less inhibited away from their home community rules, friends, and lovers, and recommended that health prevention programs focus on helping circuit party participants maintain safer practices both within and outside of their local communities.
3. Colfax et al also suggest that prevention programs should educate gay/bisexual men who attend circuit parties about the risks of drug use and associated high-risk sexual behavior. They believe that prevention programs should also target HIV-positive men, who reported in their study engaging in more unprotected sex, in order to reduce the behaviors that place others at risk for HIV. This includes practicing safer sex and being open about their HIV status with their sexual partners.

Klitzman et al also noted that MDMA users often feel it is safe to use this drug because they believe it is non-addictive.[8] Prevention activities could include distributing facts about MDMA's toxicity, about which club or party event participants may not be aware. Halkitis et al wrote that interventions to reduce methamphetamine use will not be effective until addiction specialists and researchers look at the underlying sexual motivations that promote the use of the drug. Since the drug is viewed as a powerful aphrodisiac that prolongs sexual enjoyment, what can gay men do to replace this drug? Is drug use worth the risks they are taking?[27]

Harm reduction approaches accept that many individuals will probably continue to attend raves and circuit parties, and use drugs as well as continue to engage in sexual activity at these events. They hope to lessen the harm that occurs at such events by promoting safe behaviors.

Ryan and colleagues studied the relationship between substance use disorders and risk of HIV infection in gay men, and suggested the following strategy: Community-based HIV risk reduction programs need to target heavy substance users by developing active outreach programs that go into bars and clubs and have booths at raves and circuit parties to recruit participants for multi-session cognitive-behavioral intervention programs. These sessions should include strategies for reducing the use of alcohol and other drugs.[54]

Weir, and Dillon and Degenhardt, suggested the following educational harm reduction messages for users of recreational drugs:[9,24]

- Encourage dancers to replenish fluids and sodium (500mL/hr if dancing, 250 mL/hr if inactive).
- Take breaks from dancing.

To help recreational drug users avoid drug overdosage and illness from drug interactions, encourage patients:

- To know the risks of adulterated drugs and the inaccuracies of labels.
- To know the signs and symptoms of toxicity.
- To seek immediate medical attention if one develops signs and symptoms of drug toxicity.
- To avoid alcohol if consuming recreational drugs.
- To always eat when using GHB. Using GHB on an empty stomach causes nausea and vomiting.
- To use small doses of any drug and wait at least two hours between doses.

To advocate that organizers of raves and circuit parties are responsive to health and safety issues:

- Educate organizers about the need to have medical staff or a paramedic team on site.
- Encourage participants to insist that medical care be on site before attending an event.
- Encourage participants of raves, circuit parties and recreational drug users to care for their own health needs and to be protective of their friends:
  - Advise patients not to attend a rave or circuit party alone. Encourage patients to contract with a friend to look out for each other. (This may also help prevent date rape.)
  - Tell patients to tell their friends what they are using and to stay with them if something goes wrong.
- Advise patients that if they are taken to the hospital, not to be afraid to tell physicians and nurses what drug they used.

We would also encourage HIV-positive patients to know how party drugs will interact with Viagra and HAART to avoid life-threatening combinations.

Individuals might use drugs intravenously at circuit parties and raves. The US National Institute of Drug Abuse recommends the following harm reduction strategies if individuals are not able to stop using and injecting drugs and do not want to enter and complete drug abuse treatment:

- Do not reuse or share syringes, water, or drug preparation equipment.
- Always use a new sterile syringe to prepare and inject drugs.

- Safely dispose of syringes after one use.[55]

Harm reduction can result from effective role modeling by community leaders. An example of this is a harm reduction program that came out of the Mississippi Medical Center. In the early 1990s, Kelly and associates conducted harm reduction programs in three relatively small US cities: Biloxi, Mississippi; Hattiesburg, Mississippi; and Monroe, Louisiana. First, they identified opinion leaders among gay men and then they trained these leaders in the social skills needed to help reduce the risk of acquiring HIV within the gay community.

In all three cities, intervention reduced high-risk behavior (unprotected anal intercourse) from 15 percent to 29 percent of baseline levels. This study illustrated that by recruiting community opinion leaders, teaching them concepts of harm reduction, and how to pass this information on to others, harmful behavior can be decreased.[56]

Rave participants often have peer support groups for their parties. Some have also developed Web sites, such as raversunity.com and dancesafe.org, that have harm prevention messages. Organizations hoping to decrease harm at circuit parties might also want to determine who the opinion leaders are at these events and use these individuals to pass on safety messages and to model safer behaviors such as using condoms, not drinking alcohol along with drugs or mixing drugs, and taking breaks from dancing.

Social marketing is another method of harm reduction. Social marketing uses the elements of price, promotion, and other factors to introduce a product or behavior to the public. Social marketing of condoms is considered a key element of a global strategy to reduce AIDS. People at risk for AIDS know about condoms, but often do not use them. The Louisiana Department of Health and Hospitals' Office of Public Health hypothesized that increasing condom accessibility would increase condom use. Between 1994 and 1996, more than 33 million condoms were distributed to 93 public health clinics, 39 community mental health centers, 29 substance abuse treatment centers, and more than 1,000 businesses. An example of findings from the study show that use of condoms increased among African-American women and their partners from 28 percent in 1994 to 36 percent in 1996. Condom use increased among African-American men from 40 percent in 1994 to 54 percent in 1996.[57] Circuit parties and raves are places of heightened sexual activity. Having condoms available at these events would reduce the risk of HIV and STD transmission and would be an excellent method of harm reduction that would be low cost and effective.

Harm reduction strategies that come about from input from members of the community involved can be especially effective. Researchers from the Center for AIDS Prevention Studies at the University of California, San Francisco, developed and started an HIV prevention program in a mid-sized Oregon community, and in a similar community in Santa Barbara, California.[58] Young gay men in Eugene, Oregon, along with an advisory board made up of local community leaders, developed a program they named "The Mpowerment Project." Mpowerment taught safer sex practices through a peer-run community outreach program. The outreach activities included a publicity campaign as well as parties and social events such as bike rides and small group sessions. By using this community-based HIV harm reduction program, unprotected anal intercourse decreased from 41 percent to 30 percent in one year in the Oregon community. A peer-oriented approach to reducing recreational drug use could be developed in college communities, gay communities, circuit parties, and raves, drawing from local community members' knowledge of their peer group's beliefs, norms, and behaviors.

Harm reduction is already being instituted at some circuit parties. In 2001, in Palm Springs, California, Mayor Will Kleindienst cited concerns about drug use because of 13 overdoses at the 2001 "White Party." He had asked the City Council to consider banning the annual "White Party," which derives its name from the approximately ten thousand men who dress in mostly white clothing to attend this event. However, the city decided to allow the White Party to return to its convention center in 2002 because of the huge economic impact of the party. The organizers, to address the mayor's concerns, used harm reduction techniques and emphasized the dangers of drugs, gave out condoms, and had an ambulance waiting at the 2002 party. In 2002, there were only two overdoses at the White Party.[59]

Primary prevention methods, which aim to lower the onset of behaviors that are harmful to individuals and their communities, and harm reduction, which attempts to decrease the harm created by dangerous behaviors, both play roles in preventing and decreasing the use of party drugs, in stemming the drugs' association with high-risk sexual behaviors, and in reducing rates of HIV infection at such settings as dance clubs, raves, and circuit parties. More work needs to be done in understanding what strategies are most effective and how to best apply these concepts.

Role of the physician and allied healthcare professionals

Physicians and other healthcare professionals should become more skilled at identifying alcohol and drug abuse in their practices, become more involved in educating their patients, learn how to treat medical emergencies that are club-drug related, make more use of prevention and harm reduction strategies, and become better informed about available treatment approaches for substance abusers.

1. Identifying alcohol and drug abuse

Initially, one should assess a patient's current and past use of drugs and alcohol. This should cover types of substances used, routes of administration, frequency of use, age of first use, age of first regular intoxication, and the usual amount used, as well as the highest dose used. Drug and alcohol treatment history is also valuable information. Types of programs (inpatient, outpatient, methadone maintenance, Alcoholics Anonymous, residential treatment) as well as dates of treatment should be inquired about. A complete physical examination can provide evidence of alcohol and drug abuse, such as injection marks, nasal septum erosion, skin abscesses, ascites, and physical trauma.[60]

Brief assessment tools such as the Alcohol Use Disorders Identification Test (AUDIT) developed by the World Health Organization[61] and the CAGE questionnaire are helpful in identifying alcoholism, the CAGE having a 96 percent specificity for two or more positive answers.[62] CAGE is a mnemonic for the following:

Have you ever felt you ought to **C**ut down drinking?

Have people **A**nnoyed you for criticizing your drinking?

Have you ever felt **G**uilty about your drinking?

Have you ever had a drink first thing in the morning (**E**ye opener)?

Blood work can be helpful in identifying stigmata of alcohol abuse, such as elevated SGOT/SGPT, GGT, bilirubin (total), and uric acid. Alcohol is frequently mixed with club drugs in nightclubs and circuit parties. Drug screens can be performed when suspicions of drug abuse are present.

2. Education to prevent possible problems

Education about the suspected role of chronic substance abuse in accelerating HIV infection and how injection drug use in particular increases overall risk, such as the risk of bacterial infections, including pneumonia and sepsis, should be undertaken. Such education should present risks for both HIV-positive and -negative drug users.[60,63]

Information about club drugs and their adverse effects, in particular their role in increasing risky sexual behavior and possible medical emergencies, can be provided through handouts and brief office consultations.

3. Treating medical emergencies caused by drug and alcohol abuse

When adolescents and young adults present with alterations of consciousness, the physician needs to consider rave-related problems such as hyperthermia, dehydration, electrolyte imbalance, and drug overdosage. The first assessment should be the ABCs (airway-breathing-circulation) and measurement of the patient's core temperature. The level of consciousness and level of hydration need to be assessed and treated as well. Active cooling may be needed. Oral charcoal and sorbitol may be used if drug ingestion occurred within 30 to 60 minutes. Serum chemistries, liver function tests, complete blood count, creatine kinase, and arterial blood gases should be ordered. A foley catheter to prevent urinary retention should be considered. The physician should treat hypertension, tachycardia, and metabolic acidosis if present. Intensive Care Unit admission with close monitoring of blood chemistries, hepatic transaminase levels and urine output should be considered. The clinician should also be alert to the possibility that the patient was a victim of sexual assault. Finally, the doctor should be able to make referrals to drug treatment once the patient is stabilized and treated.[9,11]

4. Harm reduction

The US National Institute of Alcohol Abuse and Alcoholism (NIAAA) recommends that healthy men limit their drinking to 14 drinks per week and that women limit it to seven. Men who consume an average of more than two drinks per day have higher incidences of hypertension and cancers, with problems for women beginning above an average of one drink per day.[64] Limiting alcohol use to social drinking levels may be helpful in reducing harm when not mixed with club drugs. Alcohol can interact with other party drugs in harmful and unpredictable ways, and the patient who intends to use club drugs in spite of the risks would be advised not to drink alcohol at all.

Ways in which club drug users can reduce their risk of HIV/AIDS include:

- Stopping the use and injection of club drugs.
- Using only sterile syringes if the patient continues to inject drugs.
- Using only sterile supplies and never sharing if injecting drugs continues.[55]

The physician may have HIV/AIDS patients who intend to continue to use club drugs in spite of the risks involved in drug interactions with their HAART regimen. In such cases, the physician can select antivirals that interact minimally with club drugs. For example, ritonavir should be avoided by patients who regularly use MDMA.

In some instances, community interventions that have successfully reduced high-risk sexual behavior from baseline levels utilized popular peers within a community to encourage such behaviors as:

- Keeping condoms nearby if sexually active.
- Avoiding sex when intoxicated.
- Assertively refusing unsafe sex coercions.[56]

5. Treatment strategies

Education, prevention, and harm reduction are more appropriate strategies than a treatment focus for the occasional club drug user. When patients meet criteria for alcohol or drug dependency, consider:

- Alcohol- and drug-dependent patients may benefit from a brief hospitalization to detoxify when they meet criteria for substance dependency.
- In treating alcohol dependency, naltrexone (ReVia), particularly in combination with coping skills therapy, can be effective in reducing craving.[65] Disulfiram (Antabuse) can also be helpful in motivating the alcoholic not to drink.[60]
- Treating underlying psychiatric conditions, such as clinical depression and anxiety disorders, with non-addictive medications such as SSRIs, or referring to a psychiatrist when screening has been positive for psychiatric disorders, is advisable. Referrals to a psychologist specializing in dual diagnoses (substance abuse and psychiatric disorders) for outpatient psychotherapy may also be appropriate.
- Support groups such as Alcoholics Anonymous and Narcotics Anonymous have been correlated with successful outcomes in a large-scale study[66] and can be recommended for many.
- No single treatment is appropriate for all individuals, and intervention needs to be matched to the individual's problems.[55]
- One effective treatment is a cognitive-behavioral therapy known as relapse prevention. Relapse prevention focuses on the identification of the individual's high-risk situations for alcohol and drug abuse and on learning coping strategies that can take the place of the substances.[67,68]
- The physician or allied healthcare professional can increase his or her skills to motivate the substance abuser to seek out help by learning motivational interviewing skills.[69,70]
- Additional information can be gathered from www.nida.nih.gov/drugpages.htm, and www.clubdrugs.org.
- Other Web sites of interest for harm reduction messages are: www.raversunity.com and www.dancesafe.org.

By utilizing some of the above approaches, physicians and other healthcare professionals can better assess and counsel the patient who is using or is considering using club drugs as part of their recreational activities.

Conclusions

Much evidence is available to support the association between club drugs and high-risk sexual behaviors. Documentation showing how such behavior leads, in turn, to higher rates of HIV infection is available almost exclusively for the gay and bisexual community. Not much is known about the high-risk sexual behaviors associated with club drug use among the largely heterosexual ravers. Club drugs themselves have other serious medical consequences for their users, gay or heterosexual, and are particularly dangerous for the HIV/AIDS patient on HAART because of possible drug interactions and adherence problems. Prevention and harm reduction approaches can be helpful in protecting persons thinking of or engaging in club drug use. Physicians and other healthcare professionals can play a role in assessing, supporting, and counseling the at-risk patient by providing education and options even when the patient is not inclined to make the same choices that the professional would have made. ■

Alan Cooper has a private practice of clinical psychology in Arlington, Garland, and Rockwall, Texas, as an associate of The Lakewood Group. Jan Swanson has a private practice of internal medicine in Arlington, Texas. Cooper and Swanson are coauthors of The Complete Relapse Prevention Skills Program *published by Hazelden Educational Materials.*

References

1. Drug Enforcement Administration. An overview of club drugs. *Drug Enforcement Administration* February 2000:1-10.
2. Rhodes F, Deren S, Wood MM, Shedlin MG et al. Understanding HIV risks of chronic drug-using men who have sex with men. *AIDS Care* 1999;11:629-648.
3. Doherty MC, Garfein RS, Monterroso E et al. Correlates of HIV infections among young short-term injection drug users. *AIDS* 2000;14:717-726.
4. Blumenthal RN, Kral AH, Gee L, Lorvick J et al. Trends in HIV seroprevalence and risk among gay and bisexual men who inject drugs in San Francisco, 1998 to 2000. *JAIDS* 2001;28264-269.
5. Strathdee SA et al. Sex differences in risk factors for HIV seroconversion among injection drug users. *Arch Internal Med* 2001;161: 1281-1288.
6. Leshner, Al. A club drug alert. *NIDA Notes* 2000;14:3-4.
7. Stall R, Paul JP, Greenwood G, Pollack LM, et al. Alcohol use, drug use and alcohol-related problems among men who have sex with men: The Urban Men's Health Study. *Addiction* 2001;96:1589-1601.
8. Klitzman RL, Greenberg JD, Pollack LM, Dolezal C. MDMA ("Ecstasy") use, and its association with high-risk behaviors, mental health, and other factors among gay/bisexual men in New York City. *Alcohol and Drug Dependence* 2002;66:115-125.
9. Weir E. Raves: A review of the culture, the drugs and the prevention of harm. *Canadian Medical Association Journal* 2000;162:1843-1848.
10. Tong T, Boyer EW. Club drugs, smart drugs, raves, and circuit parties: An overview of the club scene. *Pediatric Emergency Care* 2002;18: 216-218.
11. Rieder MJ. Some light from the heat: Implications of rave parties for clinicians. *Canadian Medical Association Journal* 2000;162:1829-1830
12. Guzman R. Circuit parties. *Focus* March 2001:4-6.
13. Mansergh G, Colfax GN, Marks G et al. The Circuit Party Men's Health Survey: Findings and implications for gay and bisexual men. *American J Public Health* 2001;91:953-958.
14. Klitzman RL, Pope HG, Hudson JI. MDMA ("Ecstasy") abuse and high-risk sexual behaviors among 169 gay and bisexual men. *Am J Psychiatry* 2000;157:1162-1164.
15. Holcomb R. Personal Communication. August 2002.
16. Office of National Drug Control Policy. Club drugs. Source: www.whitehousedrugpolicy.gov/drugfact/club/index.html; May 2002.
17. Webb E., Ashton CH, Kamali F. Alcohol and drug misuse in UK university students. *Lancet* 1996;348:922-925.
18. Winstock AR, Griffiths P, Stewart D. Drugs and the dance music scene: A survey of current drug use patterns among a sample of dance music enthusiasts in the UK. *Drug and Alcohol Dependence* 2001;64:9-17.
19. National Institute of Drug Abuse. Club drugs. *Community Drug Alert Bulletin.* Source: http://165.112.78.61/ClubAlert/ClubdrugAlert.html 2002.
20. Mathias R, Zickler P. NIDA conference highlights scientific findings on MDMA/Ecstasy. *NIDA Notes* 2001;16:1-12.
21. Henry JA, Jeffreys KJ, Dawling S. Toxicity and deaths from 3,4-methylenedioxymethamphetamine ("Ecstasy"). *The Lancet* 1992;340:384-387.
22. Mathias R. The many faces of MDMA use challenge drug abuse prevention. *NIDA Notes* December 2001;16:9-14.
23. Whitten L. Conference highlights increasing GHB abuse. *NIDA Notes* May 2001;16:10-11.
24. Dillon P, Degenhardt L. Ketamine and GHB: New trends in club drug use? *J Substance Abuse* 2001;6:11-15.
25. Zickler P. NIDA launches initiative to combat club drugs. *NIDA Notes* March 2000;14:1-5.
26. Jansen KLR. *Ketamine, Dreams, and Realities.* Florida: Multidisciplinary Association for Psychedelic Studies; 2000.
27. Halkitis PN, Parsons JT, Stirratt MJ. A double epidemic: Crystal methamphetamine drug use in relation to HIV transmission among gay men. *J Homosexuality* 2001;41:17-35.
28. Reback CJ. The social construction of a gay drug: Methamphetamine use among gay and bisexual males in Los Angeles. Report funded by the city of Los Angeles (Contract#93427) 1997.
29. Kim AA, Kent CK, Klausner JD. Increased risk of HIV and sexually transmitted disease transmission among gay or bisexual men who use Viagra, San Francisco 2000-2001. AIDS 2002;16:1425-1428.
30. Aldridge J, Measham F. Sildenafil (Viagra) is used as a recreational drug in England. *British Med J* 1999;318:669.
31. Crosby GM, Stall R, Paul JP, Barrett DC, Midanik LT. Condom use among gay/bisexual male substance abusers using the timeline follow-back method. *Addictive Behaviors* 1996;21:249-257.
32. Dolezal C, Meyer-Bahlburg HFL, Remien RH, Petkova E. Substance use during sex and sensation seeking as predictors of sexual risk behavior among HIV+ and HIV- men. *AIDS and Behavior* 1997;1:19-28.
33. Van de Ven P, Campbell D, Kippax, S et al. Factors associated with unprotected anal intercourse in gay men's casual partnerships in Sydney, Australia. *AIDS Care* 1997;9:637-649.
34. Paul JP, Stall R, Davis F. Sexual risk for HIV transmission among gay/bisexual men in substance abuse treatment. *AIDS Education and Prevention* 1993;5:11-24.
35. Catania JA, Coates TJ, Kegeles S, et al. Condom use in multi-ethnic neighborhoods of San Francisco: The population-based AMEN (AIDS in Multi-Ethnic Neighborhoods) study. *American J Public Health* 1992;82:284-287.
36. Vittinghoff E, Buchbinder SP, Judson F, McKiman D, MacQueen K. Per-contact risk of HIV associated with four types of homosexual contact. Paper presented at the Fifth Annual Conference of Retroviruses and Opportunistic Infections. Chicago, IL 1998.
37. Shoptaw S, Reback CJ, Frosch DL, Rawson RA. Stimulant abuse treatment and HIV prevention. *J Addictive Diseases* 1998;17:19-32.
38. Dolezal C, Carballo-Dieguez A, Nieves-Rosa L, Diaz F. Substance use and sexual risk behavior: Understanding their association among four ethnic groups of Latino men who have sex with men. *J Subst Abuse* 2000;11:323-336.
39. Ostrow DG, Beltran ED, Joseph JG, et al. Recreational drugs and sexual behavior in the Chicago MACS/CCS cohort of homosexually active men. *J Subst Abuse* 1993;5:311-325.
40. Chaisson J, Stoneburner R, Hildebrandt D, et al. Heterosexual transmission of HIV-1 associated with the use of smokable freebase cocaine (crack). *AIDS* 1991;5:1121-1126.
41. Colfax GN, Mansergh G, Guzman R, Vittinghoff E, et al. Drug use and sexual risk behavior among gay and bisexual men who attend circuit parties: A venue-based comparison. *JAIDS* 2001;28:373-379.
42. Mattison AM, Ross MW, Wolfson T, Franklin D. HNRC group circuit party attendance, club drug use, and unsafe sex in gay men. *J Subst Abuse* 2001;13:119-126.
43. Chesney MA, Barrett DC, Stall R. Histories of substance abuse and risk behavior: Precursors to HIV seroconversion in homosexual men. *American J Public Health* 1998;88:113-116.
44. Pau AK. Polypharmacy problems: Drug interactions in the multidrug therapy of HIV infection. Source: www.hiv-druginteractions.org January 2002.
45. Henry JS, Hill IR. Fatal interaction between ritonavir and MDMA. *The Lancet* 1998;352:1751-1752.
46. Horn G. Party favors. *Poz* 1998:90.
47. Harrington RD, Woodward J, Hooton TM, Horn JR. Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and gamma-hydroxybutyrate. *Arch Intern Med* 1999;159: 2221-2224.
48. Khalsa J, Genser S, Vocci F, Francis H, Bean P. The challenging interactions between antiretroviral agents and addiction drugs. *American Clinical Laboratory* April 2002:10-13.
49. Halkitis PN, Kutnick AH, Borkowski T, Parsons JT. Adherence to HIV medications and club drug use among gay and bisexual men. 2002 XIV International AIDS Conference 2002.
50. Lucas GM, Cheever LW, Chaisson RE, Moore RD. Detrimental effects of continued illicit drug use on the treatment of HIV-1 infection. *JAIDS* 2001;27:251-259.
51. Saunders DS, Lancee WJ, Rourke SB. The effect of alcohol and drug use on HAART adherence. Source: www.pulsus.com/cahr/abs/abs222.htm Oral presentation. 2001.
52. Freedman AM, Kaplan HI, Sadock BJ. *Modern Synopsis of Psychiatry.* Baltimore: The Williams and Wilkins Co., 1972.
53. Duncan DF, Nicholson T, Clifford P, Hawkins W, Petosa R. Harm reduction: An emerging new paradigm for drug education. *J Drug Education* 1994;24:281-290.
54. Ryan CM, Huggins J, Beatty R. Substance use disorders and the risk of HIV infection in gay men. *J Stud Alcohol* 1999;60:70-77.
55. National Institute of Drug Abuse. Principles of HIV prevention in drug-using populations. NIH Publication No. 02-4733:2002;1-32.
56. Kelly JA, St. Lawrence JS, Diaz Y, et al. HIV risk reduction following intervention with key opinion leaders of population: An experimental analysis. *American J Public Health* 1991;81:168-171.
57. Cohen DA, Farley, TA, Bedimo-Etame JR, et al. Implementation of condom social marketing in Louisiana, 1993 to 1996. *American J Public Health* 1999;89:204-208.
58. Kegeles SM, Hays RB, Coates TJ. The Mpowerment project: A community-level HIV prevention intervention for young gay men. *American J Public Health* 1996;86:1129-1136.
59. Leinwand D. Worries crash "circuit parties." *USA Today* June 20, 20.
60. Hsu JH. Substance abuse and HIV. *The Hopkins HIV Report* July 2002:1-11.
61. Babor TF, Grant M. From clinical research to secondary prevention: International collaboration in the development of the Alcohol Use Disorders Identification Test (AUDIT). *Alcohol Health and Research World* 1989;13:371-374.
62. Bradley KA, Boyd-Wickizer J, Powell SH, Burman ML. Alcohol screening questionnaires in women. *JAMA* 1998;280:166-171.
63. Selwyn PA, Alcabes P, Hartel D, et al. Clinical manifestations and predictors of disease progression in drug users with human immunodeficiency infection. *New Eng J Med* 1992;327:1697-1703.
64. National Institute on Alcohol Abuse and Alcoholism. *The Physician's Guide to Helping Patients with Alcohol Problems.* Bethesda, MD: 1995, NIH Publication No. 95-3769.
65. Garbutt JC, West SL, Carey TS, et al. Pharmacological treatment of alcohol dependency: A review of the evidence. *JAMA* 1999; 281:1318.
66. Project MATCH Research Group. Matching alcoholism treatments to client heterogeneity: Project MATCH post-treatment drinking outcomes. *J Stud Alcohol* 1997;58:7-29.
67. Marlatt GA, Gordon JR. *Relapse Prevention: Maintenance Strategies in the Treatment of Addiction Behaviors.* New York: The Guilford Press, 1985.
68. Swanson J, Cooper A. The role of alcohol and drug relapse prevention in the treatment and prevention of HIV disease. *J Int Assoc Phys AIDS Care* 1998.
69. Rollnick S, Bell A. Brief motivational interviewing for use by the non-specialist. In Miller WR, Rollnick S (Eds.) *Motivational Interviewing.* New York, NY: The Guilford Press, 1991.
70. Baker A, Dixon J. Motivational interviewing for HIV risk reduction. In Miller WR, Rollnick S (Eds.) *Motivational Interviewing.* New York, NY: The Guilford Press, 1991.

Honoring Our Heroes 2002

The International Association of Physicians in AIDS Care (IAPAC) recognized four leaders in the global battle against the AIDS pandemic during its annual Honoring Our Heroes tribute event held in Chicago, October 26, 2002, to coincide with the 40th Annual Meeting of the Infectious Diseases Society of America. IAPAC presented individual Hero In Medicine awards to three physicians who have long been in the fore of the struggle both within their respective countries and internationally, and also honored activist Zackie Achmat, in absentia, with the Jonathan Mann Health Human Rights Award.

As noted in the remarks given by IAPAC President/CEO José M. Zuniga, all four honorees are united by their respective efforts to bring the effective treatment that is now the standard in wealthier nations to HIV-infected men, women, and children in the developing world.

"The common thread connecting tonight's four honorees is that…[t]hey are each working for improved HIV treatment in the countries and regions of the world where it is most desperately needed," Zuniga said. "Tonight's four honorees embody IAPAC's mission. They are working for solutions that recognize the dignity and sanctity of every life. Thus, they are natural choices for IAPAC's highest distinctions."

F. James Muller, who received one of the Hero In Medicine Awards, is head of the Metropolitan Department of Medicine in Pietermaritzburg (KwaZuluNatal, South Africa), administering hospitals in which as many as half of the patients are HIV-positive.

Another Hero in Medicine, George Janossy, professor at the Royal Free and University College Medical School (London, UK), has pioneered research into monitoring the progression of HIV infection; he also founded the organization AffordCD4—a collective of international HIV diagnostics specialists—in an effort to make such monitoring possible in resource-limited settings.

John G. Bartlett, Chief of Infectious Diseases at Johns Hopkins University's School of Medicine (Baltimore, Maryland, USA) and IAPAC's third 2002 Hero in Medicine, is renowned both within the United States and globally for his contributions to HIV research and clinical practice. Of additional note, Bartlett continues to collaborate with IAPAC in development of the Global AIDS Learning & Evaluation Network (GALEN), most recently assuming the role of Co-Chair of the GALEN Certification Committee along with Peter Mugyenyi of the Joint Centre for Clinical Research, in Kampala, Uganda.

Achmat's physical presence was missed at Honoring Our Heroes, but the spirit of sacrifice and commitment he represents was evident. Engaged in a "medication strike," Achmat, who is himself HIV-infected, is refusing antiretroviral treatment until southern African governments institute feasible plans to make antiretroviral drugs available to all who need them.

As a leader of South Africa's Treatment Action Campaign, and a founding member of the Pan-African HIV/AIDS Treatment Action Movement, he has worked tirelessly, and effectively, to bring about such changes. Because complications of his illness made traveling to Chicago inadvisable, Achmat received the Jonathan Mann award from Mulamba Diese, Executive Director of IAPAC's Southern Africa Regional Office (IAPAC-SARO), in a special ceremony held in Johannesburg in November, 2002. ■

IAPAC 2002 Heroes In Medicine, George Janossy, F. James Muller, and John G. Bartlett (from left to right) after the awards presentation.

IAPAC President/CEO José M. Zuniga presents F. James Muller with his 2002 Hero in Medicine Award.

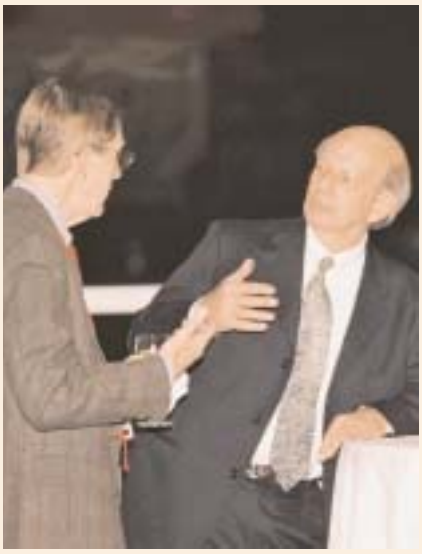
Honoring Our Heroes 2002

Before the presentation, three 2002 Hero in Medicine awards and a Jonathan Mann Health Human Rights award rest on a table atop the dais at the Hyatt Regency-McCormick Place.

During the reception, long-time IAPAC member Alejandro Guerrero, of Mérida, in Mexico's Yucatan province, examines one of IAPAC's new GRIP Guides.

José M. Zuniga, IAPAC President/CEO, delivers his remarks. Before presenting the evening's awards, Zuniga spoke on the need to increase commitment to expanding top-quality HIV treatment around the world.

Hero in Medicine George Janossy (right) speaks with Frank Mandy of Canada's National Laboratory for HIV (Ottawa). Mandy has been active with Janossy in the Afford CD4 program.



Hero in Medicine John G. Bartlett in conversation with Honoring Our Heroes reception attendees.

Looking to 2003

Continued from page 327

supplements focusing on pressing clinical management issues such as HIV-related anemia, once-daily dosing of antiretroviral regimens, and the psychiatric manifestations of HIV disease and treatment.

Rounding out the association's medical education mandate was the IAPAC Sessions 2002 held May 16-17, 2002, in Chicago; as well as IAPAC's 5th International Conference on Healthcare Resource Allocation for HIV/AIDS held April 15-17, 2002, in Rio de Janeiro. Each of these events, the proceedings of which were presented in 2002 issues of the *IAPAC Monthly* and on the IAPAC Web site, were important vehicles in harnessing the collective strength and knowledge of our global members and partners.

While I am quite pleased with the progress that the association was able to make in both its advocacy and medical education missions, what most excites me about 2002 was the significant expansion of IAPAC's technical assistance function. This year witnessed the final development of our Global AIDS Learning & Evaluation Network (GALEN) curriculum, as well as the publication of our first two learning modules: GALEN Modules No. 8 and 9—Introduction to Antiretroviral Therapies, and Antiretroviral Therapy in Resource-Limited Settings, respectively. Field-testing of these modules in Ethiopia and South Africa confirmed for IAPAC the desperate need for these medical education materials, and further committed the association to completing the entire series of GALEN learning modules in early 2003.

This year also saw the establishment of a corresponding GALEN "HIV Care Specialist" certification process—a process designed to document the core competencies of HIV-treating physicians in resource-limited settings, and to further empower this network of specialists to advocate increased resources for the provision of HIV care along a continuum. With the GALEN Certification Committee to be finalized in early January 2003, the certification process that will be overseen by Committee Co-Chairs John G. Bartlett (Johns Hopkins University, Baltimore) and Peter Mugyenyi (Joint Clinical Research Centre, Kampala, Uganda) is well on track.

IAPAC's Southern Africa Regional Office (SARO) in Johannesburg, South Africa, greatly expanded its activities in 2002, training physicians and allied healthcare professionals in southern and eastern Africa through Pfizer's Diflucan Partnership Program. To date, 10,000-plus healthcare providers in 12 countries have been trained in the administration of Pfizer-donated Diflucan, and in the prophylaxis and management of opportunistic infections. Further, IAPAC-SARO successfully re-launched I-Med Exchange, our Web-based training vehicle that had fallen dormant in late-2001 because of a host of technical and infrastructure challenges experienced in host countries.

No less important have been IAPAC's membership recruitment, retention, and services activities. Recruitment efforts yielded a significant increase in dues-paying individual memberships across a number of healthcare professions. Our retention efforts secured an 80 percent retention rate for individual dues-memberships, as well as (remarkably in this economy), 100 percent retention of IAPAC's Corporate Partners. And, IAPAC significantly expanded member services with the launch of a "Members Only" section of our Web Site, as well as a toll-free "helpline" for US-based members—1-866-IAPAC-HQ. I speak to our membership activities because, as our membership slogan clearly communicates, there is "Strength in Numbers."

Although this past year makes me particularly proud, there remains much to be done. One need only mull over the following statistic—43 million men, women, and children living with HIV/AIDS—to understand why. Looking toward 2003, I am inspired by what IAPAC, with the support of our members and partners, is poised to accomplish.

With respect to medical education, IAPAC has committed to distribute an additional 30,000-plus sets of GRIP Guides and 50,000 copies of our popular "antiretroviral agent poster," both based on the amended 2003 US DHHS "Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents." In addition, IAPAC plans to distribute European-appropriate versions of the GRIP Guides and antiretroviral agent poster based on the "European Guidelines for the Clinical Management and Treatment of HIV-Infected Adults." And, we plan to distribute GRIP Guides for physicians/patients in resource-limited settings based upon public health-inspired guidelines released earlier this year by the World Health Organization (WHO).

IAPAC pledges continued comprehensive coverage of salient issues in each of our flagship publications, the *IAPAC Monthly* and *JIAPAC*. And, the host of clinical, policy, and member services and information that are available via www.iapac.org will expand significantly in the coming year.

Our conference/symposia calendar reflects further commitment to uphold critical medical education and advocacy activities. Co-chaired by Diane Havlir (University of California San Diego School of Medicine, San Francisco) and Renslow Sherer (Cook County Hospital, Chicago), the IAPAC Sessions 2003 is scheduled to take place May 13-15, 2003, in Chicago. And the 6th International Conference on Healthcare Resource Allocation for HIV/AIDS will take place October 13-15, 2003, in Washington, DC. Information about both of these events will be available on the IAPAC Web site in early 2003.

The association is also committing to expanded participation in key policy and international coalitions and working groups—including the International HIV/AIDS Treatment Access Coalition (ITAC)—to advocate for expanded global access to a continuum of HIV care, including antiretroviral therapy. IAPAC will continue to assert our position on the need for quality assurance by insisting upon global provisions that commit governments and international institutions to measures ensuring quality care, treatment, and support for all people living with and at risk of HIV infection.

What offers greatest promise for both IAPAC and those in whose service we operate, will be the association's expanding technical assistance and capacity-building agenda. Completion early in the year of both the full GALEN curriculum, as well as the GALEN Certification Examination, will enable IAPAC to greatly enhance physician training and the documentation of care capacity in resource-limited settings by mid-2003. This medical education and certification program holds immense potential to make an immediate impact upon the care provided to HIV patients and to provide additional impetus to the drive to expand access to antiretroviral therapy.

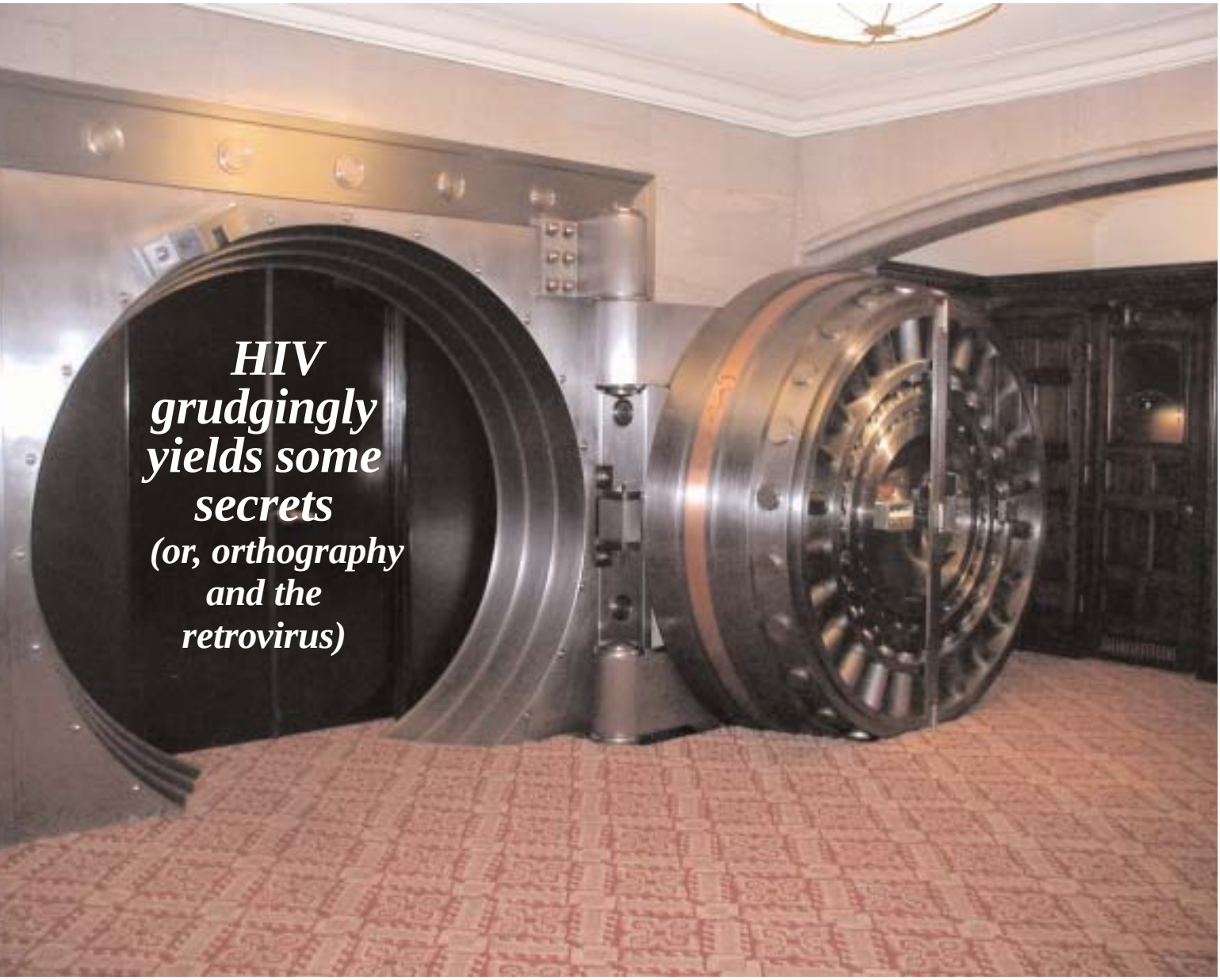
IAPAC-SARO recently committed to a renewed and expanded training contract for 2003 through the aforementioned Diflucan Partnership Program. As of early 2003, IAPAC-SARO will be training thousands more healthcare providers in an additional 11 countries within southern, eastern, and central Africa, bringing to 23 the number of countries on the African continent in which IAPAC provides direct technical assistance. Additionally, IAPAC-SARO will expand the I-Med Exchange, while broadening its information distribution and resource network throughout the southern Africa region.

And, with a need to expand our global reach, IAPAC will actively invest in our newly established European Regional Office (IAPAC-EURO) in Paris, as well as in activities throughout Latin America/Caribbean and Southeast Asian regions—where IAPAC hopes to establish a regional presence in coming years. A major IAPAC thrust will be to enhance our membership base so that the association will continue to represent a critical mass of physician-activists above and beyond the 12,000-plus members in 89 countries who give us our "Strength in Numbers."

As I close this report, I wish to express my gratitude to the IAPAC Board of Trustees for entrusting me with the association's helm for another three-year term. And, I wish to thank each of you for your continued support of our efforts to advocate on the behalf of people living with HIV/AIDS through serving those in whose hands the well-being of so many men, women, and children is placed—physicians, allied health professionals, and patient advocates. With your continued support and collaboration, IAPAC is willing and able to rise to the challenges and opportunities that will certainly come in 2003. In so doing, I pray that we may collectively celebrate, at this time next year, the millions of lives that we will have improved and saved, and the further dignity that we will have restored to our shared humanity.

On behalf of our Board of Trustees and staff, I extend IAPAC's sincerest wishes for a healthy 2003 and success in all of our endeavors. ■

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



HIV grudgingly yields some secrets (or, orthography and the retrovirus)

Photo by Mark Mascolini

Mark Mascolini

Orthographers—people who make a profession of studying spelling—would have been pleased with one HIV-related change at San Diego's 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC, or ICK-ack). But some other changes at this long-running conclave suggest grounds for reflection about the perceived status of HIV in the hurly-burly of infection fighting.

The orthographic plum was a sensible shift in the alphabetic ordering of ICAAC abstracts. For years HIV abstracts got grouped under I. This year the HIV crowd suffered a small jolt when flipping to the abstract book's familiar I section and finding—nothing. What? No HIV abstracts this year? Hardly. HIV jumped one rung up the abecedarian ladder to H, replacing "Virology (other than HIV)," which tumbled to V.

But that wasn't the only HIV difference between ICAAC 42 and most every other ICAAC for the past decade. HIV attendees endured another little shock when they scanned the program for the opening night session, long devoted to the notorious retrovirus. Not this year. Instead the keynote session considered vaccines, with one HIV talk by Lawrence Corey, a CDC foray into "the impact of global immunization programs," and—perhaps inevitably—a talk on "vaccines for agents of bioterrorism."

Hmm. Let's see which of the two late-breaker sessions will be the HIV session. Neither. Only five of 26 late-breakers touched on HIV, and they weren't all in the same session.

Well, at least Tony Fauci is back with a plenary lecture to update his take on HIV pathogenesis. What's this? Fauci is talking about *what*? Right. Bioterrorism. Perhaps the HIV set should be happy that the keynote session didn't focus entirely on treacherous plagues like West Nile virus or—an epidemic still limited to the US West, apparently—mad deer disease.

But HIV hasn't gone away. Globally, no one needs convincing, though patterns may be mutating if we can believe the US Central Intelligence Agency. The agency's National Intelligence Council predicts a watershed shift in the epidemic's course.[1] The devastation of southern and eastern Africa will continue, according to CIA seers, but eight years from now most infected people will live in China, Ethiopia, India, Nigeria, and Russia. Things aren't so great in the United States either, where—year after dreary year—another 40,000 people open their lymph nodes to HIV, and reports of risky escapades by already at-risk people appear in the paper weekly. But teaching abstinence without promoting needle exchange will make things better, we hear.

It's easy to get cranky about this state of affairs. So far bioterrorism has killed fewer people in the US—five—than Michael Gottlieb (four), Henry Masur (11), and Frederick Siegal (four) reported in their seminal AIDS case series of 1981.[2-4] West Nile virus has sent 198 Americans to their graves since 1999,[5] compared with 233 CDC-reported AIDS deaths in the epidemic's first three years here, 1979 through 1981.[6] (And the counting wasn't so good back then, since no one knew the disease existed.)

Despite such gripes, ICAAC has served HIV well, and HIV researchers from near and far observe the yearly haj to showcase their studies there. ICAAC's 2002 edition featured 152 reports of new HIV research, not counting studies summarized in five symposia and three caffeine-fueled Meet-the-Experts exegeses. And there's plenty of room on ICAAC's sumptuous program for topics great and small. But any hints of drift from a stern focus on the retrovirus rouse concern.

The reasons for that are simple. One, HIV continues its largely unimpeded global stampede. And two, for all the superb science HIV has inspired, it still guards key secrets as closely as thick steel once secured lock boxes at the San Diego Trust and Savings Bank (at left). When newly wealthy San Diegans lined up to lock down necklaces and notes of credit in William Templeton Johnson's nouveau Renaissance cathedral of finance, they could not suspect those notes might be worthless a year later, when the 1929 crash ignited the Great Depression. The secrets HIV guards seem more likely to retain their value, and to resist turnkey attempts to retrieve them from their safe-deposit security.

Who would have thought that Jay Levy's CD8 antiviral factor (CAF), first described in *Science*[7] only five years after Gottlieb *et al* described AIDS, would elude discovery—and even agreement about its existence[8]—for at least 16 years? Who would have imagined that in 2002 a good HIV vaccine might lie as far in the future as Gottlieb's report lies in the past?

Yet, as ICAAC showed, neither ugly possibility can be erased with confidence.

Who would have predicted, once puissant regimens rescued people from the grave's lip, that *stopping* successful therapy would be considered a reasonable—even a wise—option? Who could have foreseen, when a single protease inhibitor (PI) seemed destined to extract HIV from every T cell that mattered, that so much work would explore combining two of them, or three of them? Who would have guessed, once drug labs started spewing potent antiretrovirals, that bright clinicians who treat a deadly infectious disease would still have to debate when to start?

Yet in the Year of the Plague 2002, as ICAACers learned, those issues remain very much in play. Start with the starting debate, ably argued by Diane Havlir (University of California, San Francisco) at an ICAAC interactive session:

Table 1. Don't look at this table until you read the first part of START SMART

	You diagnose HIV infection in a 47-year-old woman with:		
You prescribe (percent of ICAAC audience voting for):	*360 CD4+ cells/mm3 and 30,000 RNA copies/mL*	*360 CD4+ cells/mm3 and 110,000 RNA copies/mL*	*205 CD4+ cells/mm3 and 26,000 RNA copies/mL*
EFV or NVP + CBV	13	40	60
EFV or NVP + TZV	3	6	8
TZV	15	19	24
Nothing. You monitor.	69	34	8

CBV = Combivir; EFV = efavirenz; NPV = nevirapine; TZV = Trizivir.
Source: Diane Havlir, Current strategies for initiation of antiretroviral therapy, 42nd ICAAC.

START SMART

One highly useful (and highly entertaining) feature of the last several ICAACs is the HIV interactive session. This year it looked like nearly 1,000 attendees packed the hall to punch keypads in response to queries from top clinical researchers. The sessions are useful for two reasons: They help treaters sharpen their clinical acumen by matching wits with experts. And they let treaters see how their peers field the same questions, and so mold opinion en masse.

ICAAC has spotlighted some skilled educators at these sessions, none more skilled than Diane Havlir, who bravely dusted off that shopworn snarler—when to start antiretroviral therapy—and showed that it remains a vibrant and critical question. She zeroed in on the group's zeitgeist by posing a simple case and modifying it twice.

1. You diagnose early—but not acute—HIV infection in a 47-year-old woman. Her CD4+ count is 360 cells/mm3, her viral load 30,000 copies/mL.
2. Same woman, same diagnosis, but the viral load is 110,000 copies/mL.
3. Ditto, ditto, but the viral load is 26,000 copies/mL and the CD4+ count 205 cells/mm3.

What do you prescribe?

a. Efavirenz or nevirapine plus Combivir*
b. Efavirenz or nevirapine plus Trizivir†
c. Trizivir
d. Nothing. You monitor.

*Combivir combines zidovudine (AZT) and lamivudine (3TC).
†Trizivir entwines AZT, 3TC, and abacavir.

Vote, then see how your colleagues answered in Table 1.

If you're like seven of 10 people in the ICAAC audience, you don't treat a newly diagnosed 47-year-old woman whose CD4+ count and viral load lie outside the *GO* box drawn by most current guidelines. Nearly the same proportion starts scribbling scrips—usually for three drugs—if that woman's viral load tops 100,000 copies/mL. And, even if her viral load is low (26,000 copies/mL), but her CD4+ count precarious (205 cells/mm3), almost everyone starts treating.

Maybe the most surprising result of this survey is that nearly one third of respondents *do* start HAART when the T-cell tally still stands above 350 cells/mm3 and the RNA assay measures a mere 30,000 copies/mL. Maybe the woman's age, 47 years, has something to do with it. Or maybe this quick-trigger 31 percent doesn't buy the advice that discretion is the better part of antiviral prescribing.

Havlir doesn't.

Showing a cartoon depicting a woman pushing the when-to-start pendulum back toward earlier intervention, Havlir explains that the woman is she.

Throw dogma to the dogs?

Waiting until the CD4+ count slides close to 200 before starting treatment may not qualify as dogma—not when a third of HIV docs lean toward earlier action. But revamped guidelines with 200 on the A side of anteroposterior and 350 on the backside come as close as Modern Science can to *ex cathedra* canon.

Diane Havlir's chief concern lies with the endpoints tallied in big cohort studies that find little advantage to starting treatment above 350 cells/mm3 versus starting between 200 and 350 cells/mm3. The much-sifted data from Robert Hogg,[9] Timothy Sterling,[10] and Matthias Egger[11] all reckon descents to AIDS or death—the endpoints—then fix their compass on the same foreboding polestar—200 cells/mm3. On the one hand, using AIDS and death as endpoints makes sense because those are the two "outcomes" everyone hopes most to outlast. But Havlir argues that a blinkered focus on these two dire denouements overlooks other benefits earlier treatment may bring:

- Fewer HIV-related diseases
- Increased energy and improved quality of life
- Improved cognition
- A better chance to benefit from strategies, like therapeutic vaccines, that require high-level viral suppression

At the same time, as authors of cohort studies themselves observe, the typical two- or three-year follow-up will miss a longer-term advantage of earlier treatment, if such an advantage were to emerge. But perhaps history is the factor that most dilutes the reliability of the when-to-start cohort studies presented so far. They involve cohorts first treated from 1996 to 1999,[9] 1996 to 2001,[10] and at a median date of December 1997 (interquartile range June 1997 to July 1998).[11] Although Sterling[10] tracked people into 2001, the median follow-up of 24 months means most of them started HAART in 1999 or earlier. So a large majority in all three studies began treatment with a musty 20th century regimen, not the more potent therapies prescribed up front today. As Havlir observed, 21st century first-line combos are also typically simpler and often more tolerable than 1998 standbys like stavudine (d4T), 3TC, and solo indinavir.

Havlir is not alone in making this point. In a long interview on antiretroviral strategies, veteran HIV clinician Howard Grossman observed that potent, simple, and safe regimens—3TC, abacavir, and tenofovir, for example—should encourage a closer look at hit-hard-but-later fiat.[12]

At ICAAC Michael Saag (University of Alabama, Birmingham) accented the increasing potency of newer combinations in a slide comparing this year's standards of care with those of the late 1990s [abstract LB1]. The elder antiretroviral mixes came from a 2001 meta-analysis of 23 clinical trials completed in the second half of the last decade.[13] This year's crop came from Saag's study of didanosine (ddI), emtricitabine (FTC), and efavirenz [abstract LB1] and a trial of d4T versus tenofovir plus 3TC and efavirenz [abstract LB2]. The simpler 2002 triple therapies won in a walk (Table 2).

Havlir's final pendulum push borrowed some muscle from two studies showing that HIV DNA—a measure of virus at its ease in resting T cells—offers another way to predict disease progression.[14,15] In 130 people not treated with combination antiretrovirals, every 10-fold higher HIV DNA level in peripheral blood mononuclear cells raised the risk of AIDS 2.62 times and death 1.84 times, independently of age at seroconversion, baseline CD4+ count, viral load, and T-cell-receptor excision circles.[14] In 292 people evaluated before the HAART era, HIV DNA predicted disease progression and death independently of RNA load and CD4+ count, and more robustly than either of those more familiar sibyls.[15] More and perhaps better tools to predict progression, Havlir proposed, could justify earlier therapy in people who need it.

Table 2. **First-line combos, vintage 2002, versus triple threats of yesteryear**

Regimens	*Viral load <50 copies/mL at week 24 (%)*
Triple therapies with a PI, NNRTI, or 3 NRTIs*[13]	54
ddI, FTC, efavirenz [Saag]	81
d4T, 3TC, efavirenz [Gallant]	81
3TC, tenofovir, efavirenz [Gallant]	82

*Meta-analysis of 23 trials completed in the late 1990s.
Sources: John Bartlett,[13] Michael Saag [abstract LB1], Joel Gallant [abstract LB2].

One oft-cited argument that Havlir mentioned only tangentially is the possibility that delayed therapy may allow ongoing immune wrack and ruin that treatment will not reverse. An enlightening study by Timothy Schacker and Ashley Haase, published after ICAAC, shows that one facet of immune decay can appear in the earliest days of infection.[16] By this measure, treatment started at 355 instead of 205 cells/mm3 would make little difference. But the study bolsters Havlir's point that sturdy progression predictors remain to be discovered.

Scrutinizing lymph node biopsies from 11 people before they started potent antiretrovirals, Schacker found that baseline lymph tissue fibrosis predicted lymphoid CD4+ levels and response to therapy. With collagen as a marker of fibrosis, he showed that the more collagen a person had before treatment, the fewer CD4+ cells that person had in the paracortical T-cell zone, where 98 percent of T cells lie ($r^2 = 0.72$, $P < 0.0001$). The amount of collagen did not correlate with pretreatment peripheral CD4+ count, pretreatment viral load, or duration or stage of HIV infection. One person had acute HIV infection, three had been infected six months or fewer, six had CD4+ counts over 200 cells/mm3 and no AIDS diagnoses,

and one had AIDS. Lower pretreatment collagen also predicted bigger peripheral CD4+ gains after six months of therapy in seven people who started antiretrovirals ($r^2 = 0.91$, $P < 0.0001$).

Schacker and colleagues believe this lymph tissue fibrosis with HIV infection "is analogous to the pathogenesis of cirrhosis in chronic active hepatitis B and C infection, wherein ongoing viral replication in hepatocytes leads to a state of chronic inflammation and fibrosis." They suggest that a pretreatment lymph node biopsy could help clinicians stage HIV disease and "provide useful information on when to initiate therapy." The researchers also think their findings suggest the need to study adjunctive anti-inflammatory therapy as a way to limit, or even reverse, damage to the paracortical T-cell zone.

The study serves as a reminder that research can pry loose HIV's secrets, but that many others remain. It also hints that the standard of care in 2006 will differ more from today's standard than today's differs from 1998's.

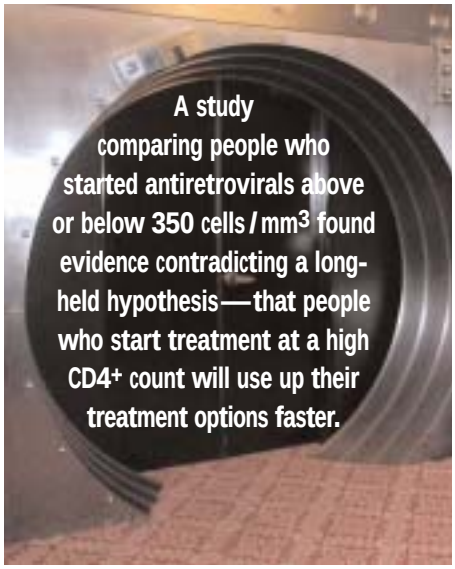
Starting early, stopping early

A prospective cohort study at ICAAC compared 112 people who took their first antiretroviral with T tallies above 350 cells/mm3 with 85 who waited until they had 200 to 350 cells/mm3 [abstract H-158]. The waiters didn't end up with AIDS faster than the early birds, reported María Perez-Elias (Ramón y Cajal Hospital, Madrid), but they switched regimens significantly more often because of virologic failure.

The early group started with an average CD4+ count of 506 cells/mm3, compared with 275 cells/mm3 in the later-starting group ($P < 0.001$). No one had an AIDS diagnosis before treatment. Although early and later starters did not differ in age (34 versus 35 years), viral load (4.8 versus 4.7 logs), or relative use of PIs and nonnucleosides (NNRTIs), the later group had three nearly significant and possibly related disadvantages:

- More injection drug users (65 versus 51 percent, $P = 0.053$)
- More with HCV coinfection (64 versus 49 percent, $P = 0.097$)
- Fewer with better than 90 percent adherence, measured by self-report and hospital pharmacy records (40 versus 50 percent, $P = 0.109$)

After 12 weeks of antiretroviral therapy, 89 percent in both groups had at least a 1-log drop in circulating virus or fewer than 400 RNA copies/mL. After one year, 86 percent in the early group and 88 percent in the later group had a sub-400 viral load. The "clinical event" rate was higher in the delayed group, but not significantly so, and that group had a trend to more frequent immune reconstitution disease than the early group (50 versus 16.7 percent, $P = 0.171$).



The critical outcome difference proved to be the rate and reasons for regimen switching. In the early group, 57 percent switched their regimen over 18 months of follow-up, compared with 67 percent in the later group, a nonsignificant trend ($P = 0.157$). But nearly three times more later starters (36 percent) than early starters (13 percent) switched because of virologic failure ($P = 0.005$). In a multivariate analysis adjusted for the three variables bulleted above, a later start independently upped the odds of switching for failure by a factor of 5 ($P = 0.003$). But injection drug use, adherence below 90 percent, and HCV coinfection each raised that risk much more, at respective odds ratios of 50 ($P = 0.016$), 37 ($P = 0.02$), and 40 ($P = 0.014$).

Because of their lower pretreatment CD4+ count, the later group also trailed the early starters in CD4+ count three, six, nine, 12, 15, and 18 months after starting therapy ($P < 0.0001$ at every point). But at 18 months they had a good average count of 525 cells/mm3, compared with 786 cells/mm3 in the early group.

Reasonable people can disagree about what this study means. Perez-Elias and colleagues offered a binocular view. "It seems safe to delay initial [antiretroviral therapy] in non-AIDS patients until the CD4+ count reaches a number between 350 and 200 cells/mm3, in terms of clinical outcomes," they concluded. "However, the higher risk of changes due to failure complicates further antiretroviral therapy management" in later starters. Indeed, the study slices some sinew from the stock argument that people who start treatment at high T-cell counts will expend their antiretroviral options faster than waiters. In this cohort, at least, the exact opposite could prove true.

Reasonable people can also turn the table and ask, if someone started treatment with a high CD4+ count, as Perez-Elias's early group did, is it safe to stop if treatment keeps HIV under wraps? Before ICAAC two studies suggested that people can stop safely if they launched their antiretroviral argosy at CD4+ and RNA sums no longer deemed grounds for intervention by the guideline givers—generally, above 350 cells/mm3 or below 55,000 copies/mL.[17,18] An ICAAC study reached the same conclusion.

Another Madrid group, represented by Manuel Fernández-Guerrero (Fundación Jiménez Díaz), tracked 49 people averaging 34 years of age who took their first antiretroviral with 300 to 500 CD4+ cells/mm3 or 10,000 to 70,000 RNA copies/mL, and usually both [abstract H-1082]. The plan of this ongoing study calls for renewed treatment if CD4+ cells tumble under the 300 line, if the viral load tops 70,000 copies/mL twice in a row, if an opportunistic disease develops, or if a person withdraws consent.

The group's average CD4+ count when they stopped treatment stood at a robust 730 cells/mm3. That average dropped rapidly in the drug holiday's first four months, to 544 cells/mm3, then drifted to 525 cells/mm3 at month eight, 496 cells/mm3 at month 12, and 481 cells/mm3 at month 16. So far 12 people (24 percent) have resumed treatment, four in the first eight months, and eight during months nine through 20. But all restarters regained virologic control with the regimen they had stopped. Only one person endured a disease suggesting compromised immunity, herpes zoster.

Predicting rebounds, predicting death

Italian clinicians and a researcher at the State University of New York offered new

Table 3. **Independent predictors of death in a cohort of 639 people with HIV infection**

	Risk factor	*Odds ratio*	*Assigned value*
Major factors	Thrombocytopenia (platelets < 130 x 10^3/µL)	5.297	17
	Glucose > 120 mg/dL	4.533	15
Intermediate factors	Viral load > 10,000 copies/mL	3.546	13
	Hemoglobin < 12 g/dL	3.304	12
	Lactate dehydrogenase > 700 U/L	2.776	10
Minor factors	HCV coinfection	2.115	8
	$CD4^+$ < 200 cells/mm^3	2.041	7
	Age > 39 years	2.032	7

Predicts 50 percent risk of death: Assigned value score > 48 *or* 2 Majors + 2 Intermediates *or* 2 Majors + 1 Intermediate + 2 Minors *or* 1 Major + 2 Intermediates + 3 Minors *or* 3 Intermediates + 3 Minors

Source: Chiu-Bin Hsiao [abstract H-1145].

angles on two other retroviral riddles—what predicts a listless $CD4^+$ rebound when restarting treatment after a drug break, and what predicts death in people with HIV infection?

Elena Seminari and colleagues at the Policlinico San Matteo in Pavia have nearly completed a one-year study that randomized people with viral loads below 50 copies/mL on treatment to continue therapy or to switch between treatment and no treatment every month. A subanalysis presented at ICAAC tried to figure why five people met the protocol criterion for leaving the study—a $CD4^+$ count below 200 cells/mm^3 after a full month on treatment following a break [abstract H-1745]. One person failed to climb back to 200 cells/mm^3 at month two, two at month four, one at month six, and one at month eight. All five shared one trait, a T-cell nadir below 50 cells/mm^3. But that deficit alone did not explain their poor $CD4^+$ recovery while on treatment, because 12 other study participants had nadirs under 50 and did not have to leave the study.

Comparing the five dropouts, the 12 others with sub-50 nadirs, and 45 study participants with nadirs above 50 cells/mm^3, Seminari found no differences in age, gender, duration of treatment, duration of viral control below 50 copies/mL, or antiretroviral regimen. The $CD4^+$ nadirs in the 17 with sub-50 nadirs averaged 23 cells/mm^3, compared with a nadir of 256 cells/mm^3 in the other 45 ($P < 0.001$). Having a nadir under 50 cells/mm^3 raised by 18 times the risk of failing to attain a count above 200 cells/mm^3 after a full on-treatment month.

The first on-treatment month after the first holiday month held the clue to protocol-defined $CD4^+$ failure. Everyone in the 45-person comparison group regained all the $CD4^+$ cells lost during the first break during their first month back on treatment. The 12 people with nadirs under 50 cells/mm^3 who did not have to leave the study regained 70 percent of their T cells in the first on-treatment month. And the five people who failed to climb back to 200 cells/mm^3 at some point in the study regained only 37 percent of their T cells in the first on-treatment month. Seminari proposed that this "flattened regain curve" in the first treatment month after the first treatment break may predict later $CD4^+$ failure.

Not surprisingly, a $CD4^+$ count under 200 cells/mm^3 emerged as one of eight predictors of death in a retrospective analysis of 67 people who died in a population of 639 with HIV infection [abstract H-1145]. But statistical analysis by Chiu-Bin Hsiao (State University of New York, Buffalo) rated a sub-200 $CD4^+$ sum as only a "minor" factor. The two major factors were a small surprise: thrombocytopenia and hyperglycemia (Table 3).

Hsiao's record review involved 417 males and 222 females seen between December 1998 and September 2001. The group included 292 African Americans, 229 Caucasians, and 90 Hispanics; 253 had HCV coinfection. After a median follow-up of two years, 47 males and 20 females had died. Forty-three of those who died (64 percent) had a $CD4^+$ count under 200 cells/mm^3, and 42 (63 percent) had a viral load above 10,000 copies/mL.

A multivariate analysis determined that a platelet level below 130 x 10^3/µL inflated the risk of death 5.3 times, followed by hyperglycemia, a viral load above 10,000 copies/mL, anemia, high lactate dehydrogenase, HCV coinfection, a $CD4^+$ count under 200 cells/mm^3, and age over 39 years (Table 3). Assigning a numeric value to each of the eight risk factors, Hsiao fashioned two schemes to reckon the risk of death.

1. If the added risk values total more than 48, the risk of death is 50 percent.
2. If a person has certain combinations of major, intermediate, and minor risk factors (as defined in Table 3), the risk of death is 50 percent.

A person with none of the risk factors has a 0.6 percent risk of death. Someone with all the risk factors has a 98 percent risk. Risk rates reflect the median follow-up of two years (range 12 to 1,245 days) for the cohort. In the 67 cohort members who died, a median of 360 days (range 12 to 904 days) elapsed between the date of data collection and death.

This kind of analysis comes with built-in limits. Although the cohort's make-up is diverse, it is relatively small and includes only 67 deaths. Substantial subsets were taking no antiretrovirals (151 or 24 percent) or only two NRTIs (66 or 10 percent). Hsiao did not report how many in those groups died, but he reported that different regimens did not influence mortality. Still, the surprise finding on thrombocytopenia and the high risk with hyperglycemia—a PI side effect—stress the value of tracking these lab values and should inspire further research.

START STRONG

As renewed debate on when to start antiretrovirals spices recent meetings, debate continues on what to start. At the XIV International AIDS Conference, Daniel Kuritzkes (Brigham and Women's Hospital, Boston) spoke for many when he distilled "a world of options" to two 99-proof favorites—a ritonavir-boosted PI or efavirenz.[19] Bristol-Myers Squibb hopes to change that by grooming atazanavir as an unboosted first-line PI with a unique resistance profile, a light touch on lipids, and a once-daily demand on memory. But an ICAAC report of a trial comparing the new PI with efavirenz will take some explaining before atazanavir catches on as prime-time primary therapy. And although

Table 4. **Atazanavir matches efavirenz at 48 weeks, *but* . . .**

	Atazanavir (400 mg)	*Efavirenz (600 mg)*	*P*
n	404	401	
Completed 48 weeks (%)	84	80	NS
Discontinued with toxicity (%)	6	8	NS
Grade 2-4 toxicity (%)	41	45	NS
Lost to follow-up (%)	4	4	NS
<400 copies/mL (N = F) (%)	70	64	NS
<50 copies/mL (N = F) (%)	32	37	NS
<400 copies/mL (as treated) (%)	84	81	NS
<50 copies/mL (as treated) (%)	51	54	NS
CD4+ increase (cells/mm^3)	176	160	0.001

N = F: noncompleter-equals-failure analysis.
Source: Kathleen Squires [abstract 1076].

triple nucleoside combos centered on abacavir rate first-line consideration among many clinicians, one abacavir medley rehearsed at ICAAC fell flat. Other studies pitted ritonavir-boosted PIs against each other and against efavirenz, and efavirenz didn't suffer in the comparison.

Atazanaverities

The biggest surprise at ICAAC came in the 48-week results of a multinational, randomized, placebo-controlled comparison of atazanavir and efavirenz presented by Kathleen Squires (University of Southern California, Los Angeles) [abstract H-1075]. Among almost 800 people treated for close to a year, a mere 32 percent taking atazanavir (plus AZT and 3TC) had a viral load under 50 copies/mL in a noncompleter-equals-failure analysis. Maybe even more shocking, only 37 percent taking efavirenz with the same NRTIs hit the sub-50 target. Whatever went wrong?

The study involved treatment-naive people in Asia, Africa, Europe, and North and Central America with a median baseline viral load around 4.9 logs (about 80,000 copies/mL). More than 40 percent had a viral load over 100,000 copies/mL. The median starting CD4+ count measured 286 cells/mm^3 in the atazanavir arm and 280 cells/mm^3 in the efavirenz arm. The cohort was young, with a median age of 34 years. About one third of study participants were women.

The noncompleter-equals-failure analysis counted failure as stopping the assigned treatment for any reason, an AIDS diagnosis, or a confirmed rebound above 50 copies/mL after a response. More than 80 percent in both groups finished 48 weeks of treatment. But at that point only one third of study participants had a viral load under 50 copies/mL by the intent-to-treat analysis and only half had a sub-50 load in an on-treatment analysis (Table 4). The small differences between treatment arms did not reach statistical significance. Although the atazanavir group gained significantly more CD4+ cells than the efavirenz group, Squires reasonably proposed that the modest difference probably has no clinical relevance.

One third in the atazanavir group had hyperbilirubinemia, but only 5 percent had to lower their atazanavir dose and fewer than 1 percent left the trial as a result. As in other atazanavir trials, fasting lipids changed little with the drug over 48 weeks. People taking efavirenz had bigger lipid jumps, but few people crossed National Cholesterol Education Program (NCEP) thresholds for antilipid therapy.

Some factor or factors clearly sabotaged the virologic response to both drugs in this study. Although research has yet to establish the potency of atazanavir, efavirenz has an unblemished record in head-to-head trials that enroll treatment-naive people. In a study of efavirenz plus 3TC with either tenofovir or d4T, for example, 48-week proportions with viral loads under 50 copies/mL measured over 80 percent in a missing-data-equal-failure analysis [see abstract LB2 below]. Reason dictates that efavirenz did not suddenly become a rotten drug.

A few factors could contribute to the dreadful virologic results. The protocol forbade dose reductions with AZT or 3TC or switches to different nucleosides. Those dictates may have spawned spotty adherence reflected in emergence of the 3TC-related M184V mutation in more than half of the study participants genotyped so far. Poor adherence seems even more likely when one considers that the nonnucleoside-linked K103N mutation cropped up in 65 percent of those genotyped, a rate that drew stunned murmurs from the crowd. Atazanavir's apparent signature mutation, I50L, appeared in only 16 percent so far. But, as much research shows, resistance will emerge first against 3TC and nonnucleosides when a regimen begins failing.

Poor adherence apparently followed a regional pattern. Squires told *IAPAC Monthly* that virologic responses in some regions considerably lagged those in others. European participants did worse than those in Asia and Africa, she noted, surmising that a higher proportion of injection drug users in the European population may partly explain those differences. At the same time, Squires added, the relative unavailability of antiretrovirals in Africa and Asia could inspire stricter adherence among people lucky enough to get into trials.

Finally, the trial used a tougher than usual definition of failure prescribed by the Food and Drug Administration. It counts any drug switch for any reason or two consecutive viral loads above 50 copies/mL as a failure. The AIDS Clinical Trials Group, for example, requires consecutive rebounds above 200 copies/mL to signal failure, figuring that touchy ultrasensitive assays could record some 50+ readings that do not signal abiding rebounds.

Clearer answers should emerge as the researchers analyze region-specific response and resistance patterns. (The trial did not include a formal adherence measure.) Even if poor adherence and a draconian failure definition explain this downfall of atazanavir and efavirenz, clinicians will likely want fresh proof of atazanavir's antiviral punch in the wake of this study. Few are likely to demand the same for efavirenz.

If atazanavir turns out to be a notch or two feebler than hoped, a ritonavir boost could be a fallback strategy. At this point atazanavir's maker still positions the drug as an unboosted first-line agent, but Bristol researchers did study the impact of a 100-mg ritonavir prod in 30 healthy volunteers [abstract H-1716]. S. Agarwala and colleagues gave them 300 mg of atazanavir once daily for 10 days, then added ritonavir on days 11 through 20. Atazanavir's geometric mean peak concentration jumped from 3,288 ng/mL on day 10 to 6,129 ng/mL on day 20, an

86 percent gain. The area under the concentration-time curve (AUC) for atazanavir vaulted from 16,875 ng • h/mL on day 10 to 57,039 ng • h/mL on day 20, more than a threefold surge. The trough concentration climbed about 10-fold. Ritonavir levels varied little over the course of the study.

As with any drug, the danger of increased exposure is increased toxicity. In earlier studies that used 400 or 600 mg of atazanavir daily, more people taking the higher dose had bilirubin elevations. And, as Bristol's Edward O'Mara reported in an analysis of 202 people enrolled in phase I studies of the PI, higher AUCs raised the risk of billowing bilirubin regardless of whether a person has a genotype favoring hyperbilirubinemia [abstract A-1253]. At the same time, a 7/7 genotype in the UGT 1A1 gene independently raised the risk that total bilirubin would exceed 2.5 mg/dL. (UGT 1A1 glucuronidates unconjugated bilirubin.) Eleven of 13 people (85 percent) with the 7/7 genotype had a total bilirubin topping 2.5 mg/dL, compared with 17 of 49 (35 percent) with a 6/7 genotype and eight of 62 (13 percent) with a 6/6 genotype.

Analyzing 950 isolates from people with PI experience but naive to atazanavir, Bristol's Richard Colonno found that most isolates resistant to one or two PIs remained susceptible to atazanavir when he used an arbitrary 3-fold drop in susceptibility to indicate resistance [abstract H-2049]. But most isolates resistant to three or more PIs also proved resistant to atazanavir. The analysis broke down like this:

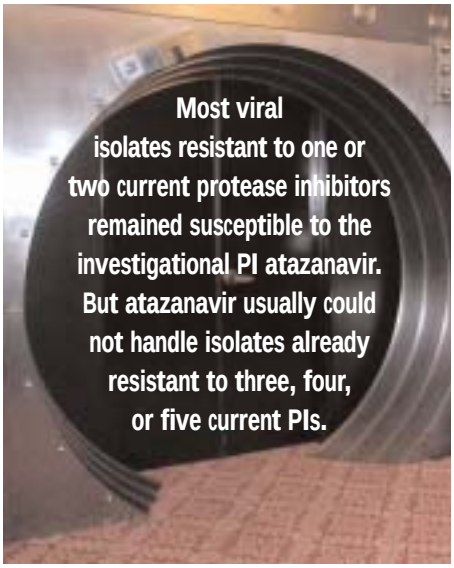
- Among 157 isolates resistant to amprenavir, nelfinavir, ritonavir, or saquinavir, 138 (88 percent) remained susceptible to atazanavir.
- Among 57 isolates resistant to ritonavir *and* amprenavir, indinavir, nelfinavir, lopinavir, or saquinavir, or resistant to amprenavir and lopinavir, or nelfinavir and saquinavir, or nelfinavir and indinavir, 46 (81 percent) remained susceptible to atazanavir.
- Among 99 isolates resistant to three PIs, 34 (34 percent) remained susceptible to atazanavir.
- Among 96 isolates resistant to four PIs, 15 (16 percent) remained susceptible to atazanavir.
- Among 142 isolates resistant to five PIs, 7 (5 percent) remained susceptible to atazanavir.

Colonno also figured which mutations in these isolates conferred resistance to atazanavir. No single mutation did, but any five from the following familiar 14 did:

10I/V/F	20R/M/I	24I	33I/F/V	36I/L/V	46I/L	48V
54V/L	63P	71V/T/I	73C/S/T/A	82A/F/S/T	84V	90M

Two PIs vs two PIs vs efavirenz

Despite the mysteriously sad showing of efavirenz in its contest with atazanavir (above), it did quite nicely, thank you, against once-daily saquinavir/ritonavir [abstract H-167]. The FOCUS study randomized 161 treatment-naive people with



a mean viral load around 4.75 logs (about 56,000 copies/mL) to start standard-dose efavirenz or 1,000 mg of saquinavir plus 100 mg of ritonavir once a day. Clinicians picked two nucleosides to go with the main course, and principal investigator Julio Montaner (University of British Columbia, Vancouver) did not report the NRTI breakdown in each arm. People came into the study with $CD4^+$ counts averaging 371 cells/mm^3 in the saquinavir group and 339 cells/mm^3 in the efavirenz group.

An intent-to-treat analysis at week 48 considered all study participants who took their assigned drugs and had at least one on-drug RNA rating. By that measure, 51 percent taking saquinavir and 71 percent taking efavirenz notched a viral load below 50 copies/mL. The saquinavir group did better in an on-treatment analysis, but still lagged the efavirenz group, with 73 versus 93 percent under 50 copies/mL. The study tested the hypothesis that saquinavir/ritonavir is "noninferior" to efavirenz in pushing viral loads under 50 copies/mL. "Noninferiority criteria," Montaner reported, "were not met."

Gastrointestinal (GI) side effects proved the PIs' undoing in the intent-to-treat analysis. One third of the 81 people assigned to saquinavir/ritonavir had nausea, vomiting, or diarrhea, compared with 4 percent of the 80 people randomized to efavirenz. Twelve people (15 percent) stopped saquinavir/ritonavir because of side effects and 11 (14 percent) withdrew their consent to continue. Respective numbers in the efavirenz group were five (6 percent) and three (4 percent).

Total cholesterol rose from an average 171 mg/dL at baseline to 206 mg/dL in the PI group and from 167 to 204 mg/dL with efavirenz. Triglycerides climbed from 124 to 175 mg/dL with saquinavir/ritonavir and from 139 to 210 mg/dL with efavirenz. Because research shows that d4T boosts lipids [see abstract LB2 below], knowing which NRTIs people were taking may have enlightened this lipid analysis.

Montaner proposed that the saquinavir group's GI troubles may be traced to an ingredient in saquinavir's soft-gel capsule. He suggested that the venerable hard-gel formulation may be easier to stomach with a ritonavir boost.

Another study of saquinavir/ritonavir, this time at 1,000/100 mg *twice* daily in people with or without PI experience, pitted those PIs against indinavir/ritonavir at 800/100 mg twice daily [abstract H-172]. The regimens yielded similar virologic responses, but more people had to switch from the indinavir arm than from the saquinavir arm, and more taking indinavir suffered disease progression. Two features of the MaxCmin 1 trial design complicate interpretation of the results: First, as in the FOCUS study, individual clinicians picked the NRTIs to give with the PIs; they could also add an NNRTI if deemed necessary. But chief investigator Jan Gerstoft (University of Copenhagen) did not report the non-PI treatment assignments. Second, the study population can safely be called mixed. About 40 percent in each treatment arm had no PI experience. Among those who had tried a PI, about 60 percent had a viral load under 400 copies/mL when they entered the study.

After 48 weeks of follow-up, an intent-to-treat analysis involving study participants

Table 5. **A new nucleoside roughs up d4T**

		Kaplan-Meier estimate at week 52		
Failure measure	*Definition*	*FTC (%)*	*d4T (%)*	*P*
Virologic	>400 copies/mL at week 12 or >400 after <400	4.7	14.1	<0.001
Tolerability	Discontinuation because of toxicity	6.7	13.9	0.03
Efficacy	Virologic or tolerability failure, disease progression, or loss to follow-up	19.1	35.1	<0.001

Source: Michael Saag [abstract LB1].

who took at least one assigned dose rated 20 percent taking indinavir and 18 percent taking saquinavir as virologic failures. But 41 percent randomized to indinavir/ritonavir had to stop taking those PIs compared with 27 percent randomized to saquinavir/ritonavir ($P = 0.018$). Gerstoft recorded clinical progression in 28 percent of the indinavir group and 15 percent of the saquinavir group ($P = 0.006$), with no deaths in either arm. Total cholesterol, low-density lipoprotein cholesterol, and triglycerides each rose about 20 percent with indinavir/ritonavir, but less than 10 percent with saquinavir/ritonavir ($P < 0.05$).

Another study by Jan Gerstoft appraised one familiar combination (saquinavir/ritonavir at 400/400 mg twice daily plus AZT/3TC) and two rarer hybrids (ddI/d4T/abacavir and AZT/3TC plus nelfinavir at 1,250 mg twice daily and nevirapine at 400 mg twice daily) in 178 treatment-naive people [abstract H-164]. The rationale offered for the triple-nuke regimen was that it may be less prone to cross-resistance than abacavir plus AZT and 3TC. The main outcome of the trial seems to be that half the people in each treatment arm bailed out of the study before week 48. With 60 people in each group, 33 stopped saquinavir/ritonavir, 24 nelfinavir/nevirapine, and 35 the three nucleosides.

Neurologic toxicity—presumably neuropathy—felled 16 people (27 percent) in the NRTI group compared with three taking saquinavir/ritonavir and two taking nelfinavir/nevirapine ($P < 0.001$). When compared by grade 4 toxicity rates, saquinavir/ritonavir proved the most tolerable regimen (four people), followed by nelfinavir/nevirapine (seven), and the triple nukes (eight). The NRTI regimen also lagged the others in a missing-data-equal-failure analysis of sub-20-copy viral loads at 48 weeks, with about 41 percent under that mark compared with 55 percent taking saquinavir/ritonavir and 62 percent taking nelfinavir/nevirapine. Few would contest Gerstoft's conclusion that "this triple NRTI regime cannot be recommended."

A nucleoside and a nucleotide outdo d4T

As if the past year had not brought enough bad news for d4T, the hapless nucleoside came up on the short end of head-to-head comparisons with two rookies in the class—the nucleoside emtricitabine (FTC) and nucleotide tenofovir.

FTC trounced d4T by numerous measures of efficacy in a double-blind, placebo-controlled trial involving treatment-naive people also beginning once-daily ddI plus efavirenz [abstract LB1]. FTC—a cytosine analog like 3TC—needs only one 200-mg dose daily. Michael Saag (University of Alabama, Birmingham) reported that the 286 people randomized to FTC and the 285 randomized to d4T matched closely in pre-treatment viral load (4.9 logs in both groups) and $CD4^+$ count (280 cells/mm^3 in the FTC group and 300 cells/mm^3 in the d4T group).

After 24 weeks of treatment, 81 percent taking FTC and 70 percent taking d4T had a viral load under 50 copies/mL ($P = 0.002$). FTC bettered d4T in 52-week Kaplan-Meier probabilities of efficacy, tolerability, and effectiveness, defined in Table 5. By week 52, people taking FTC had gained significantly more $CD4^+$ cells than those taking d4T.

If licensed, FTC would join ddI, 3TC, and tenofovir as nucleosides (or -tides) that can be taken once daily. Also like 3TC and tenofovir, it stifles hepatitis B virus as well as HIV. A 48-week interim analysis of another placebo-controlled trial showed similar potency with tenofovir or d4T in antiretroviral-naive people, but significantly fewer side effects with tenofovir [abstract LB2]. The 600 study participants had an average starting viral load of 4.9 logs and an average $CD4^+$ count of 279 cells/mm^3. Everyone also took 3TC and efavirenz.

Joel Gallant (Johns Hopkins University) reported similar RNA and $CD4^+$ responses with tenofovir and d4T after 48 weeks. In a missing-data-equal-failure analysis, 82 percent taking tenofovir and 81 percent taking d4T had a viral load under 50 copies/mL. Responses did not differ in subgroups starting treatment with fewer or more than 100,000 RNA copies/mL. The tenofovir group gained an average 169 cells/mm^3, compared with 167 cells/mm^3 with d4T.

Rates of grade 3 or 4 side effects proved similar in the two groups—bedeviling 19 percent taking tenofovir and 17 percent taking d4T. But the d4T group lagged tenofovir takers in three key lab measures and in peripheral neuropathy. Triglycerides rose an average 74 mg/dL in the d4T group but did not change in the tenofovir group ($P < 0.001$). Total cholesterol climbed by 53 mg/dL with d4T versus 25 mg/dL with tenofovir ($P < 0.001$). Whereas 7 percent taking tenofovir reached lactate levels above 2.1 mmol/L, 36 percent taking d4T did ($P < 0.001$). Peripheral neuropathy affected 2 percent taking tenofovir and 7 percent taking d4T ($P < 0.001$).

CHANGE STRONG

Although the ongoing comparison of tenofovir with d4T (immediately above) suggests tenofovir may be a potent, but gentler, first-line option, licensing trials cast this nucleotide reverse transcriptase inhibitor as a rescue or salvage player. Further analysis of a placebo-controlled tenofovir intensification trial, presented by Gilead's Michael Miller, pinpointed factors that favored a viral load response below 50 copies/mL [abstract H-1077].

Tenofovir allies: low load, no TAMs, M184V

The trial involved 550 people taking a stable but incompletely suppressive regimen; two thirds added once-daily tenofovir and one third added placebo. After 24 weeks 22 percent taking tenofovir reached a sub-50 viral load, compared with 1 percent in the placebo group. Miller attributed success or failure with tenofovir to two variables: baseline viral load and resistance profile. The lower the viral load when tenofovir began, the better the chance of getting under 50 copies/mL:

Percent reaching <50 copies/mL with baseline viral load of:			
<1,000 (*n* = 81)	1,000-2,500 (*n* = 99)	2,500-5,000 (*n* = 80)	>5,000 (*n* = 86)
43	27	11	6

Among people starting tenofovir with a thymidine analog mutation (the TAMs are M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E), only 11 percent attained a sub-50 viral load, whereas 49 percent without TAMs did so. Having the 3TC-induced M184V mutation also favored a good virologic response with add-on tenofovir; 49 percent with M184V at baseline got their viral load under 50 copies/mL.

In a multivariate analysis, Miller calculated the following odds ratios (OR) for a sub-50 copy reading according to baseline viral load or mutation array:

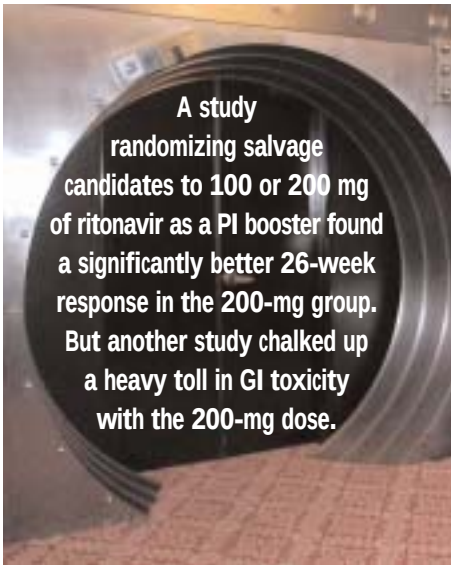
- Baseline TAMs: OR 0.14, $P < 0.0001$
- Higher baseline viral load: OR 0.24, $P = 0.0016$
- Baseline M184V: OR 3.1, $P = 0.032$

Intensification of a floundering regimen can be risky. If adding a new drug doesn't stop the slide, mutations can pile up, as Miller also demonstrated in this analysis. His findings give clinicians a few tools to help decide whether adding tenofovir is worth the risk. When tenofovir regimens did fail in this population, added TAMs proved the biggest culprit. The tenofovir-linked K65R mutation popped up in only 3 percent (eight people), and none suffered a virologic rebound.

T-20 license—and ultimate trial—loom

Enfuvirtide (T-20) seems to be sailing toward approval as the first drug in a new class since nevirapine cleared regulatory hurdles in 1996. Two big randomized studies in people with deep treatment experience showed that T-20 plus an "optimized background regimen" picked with the help of resistance testing can knock a log and a half off the viral load, easily outdoing the optimized regimen alone.[20,21] No one—least of all people with time running out and drug options running down—will look askance at the likely value of this novel antiretroviral. But one wonders how smoothly it will fit into real-world schemes.

Because T-20 is hard to make, it will cost a lot, almost certainly more than any current antiretroviral. It has to be mixed carefully a half-hour before each dose (see "T-20" in reference 12), and it must be injected under the skin twice daily. Almost everyone who uses T-20 gets injection site reactions, 98 percent in the two big randomized trials.[20,21] Although only 3 percent in those studies quit as a result, more will almost certainly abandon the drug in practice. In the European-Australian trial,[20] the overall 24-week dropout rate was 11 percent in both the T-20 group and the non-T-20 group. But in the North American-Brazilian trial,[21] 17 percent quit the T-20 arm compared with 5 percent in the control arm.



At ICAAC Julio Montaner reviewed results from the North American-Brazilian trial, looking at potential subgroup differences and at predictors of antiviral vim [abstract H-1074]. Compared with the optimized regimen alone, T-20 plus optimized background yielded a better virologic response in males and females, whites and nonwhites, people under and over 40 years old, people with baseline viral loads below or above 100,000 copies/mL, and people with starting $CD4^+$ counts below or above 100 cells/mm^3. People with phenotypic or genotypic sensitivity to zero, one to two, or three to four antiretrovirals did significantly better with T-20 than with optimized background alone ($P < 0.05$). Those with phenotypic or genotypic sensitivity to five or more antiretrovirals got a better response with T-20, but not a significantly better response.

In a multiple regression analysis estimating the log change in viral load at 24 weeks, six variables mattered:

- Treatment with T-20: -1.00 log, $P < 0.0001$
- Every additional 100 $CD4^+$ cells/mm^3 at baseline: -0.19 log, $P < 0.0001$
- Better phenotypic sensitivity score: -0.33 log, $P < 0.0001$
- Better total four-day recall adherence score: -0.25 log, $P < 0.0001$
- Lopinavir/ritonavir in the optimized background: -0.24 log, $P = 0.0348$
- Experience with lopinavir/ritonavir: +0.83 log, $P < 0.0001$

Replacing the phenotypic sensitivity score with a genotypic sensitivity score yielded similar results. Baseline viral load did not figure in the response to T-20. The interesting findings with lopinavir/ritonavir clearly indicate that T-20 does much better when it teams with a potent ally. Montaner noted, though, that the T-20 group did not differ from the control group in proportions pretreated with lopinavir or getting lopinavir in the salvage regimen.

Extra ritonavir: boost or consequences

To the metaphorically minded, ritonavir's manic career may resemble that of a high-flying matinee idol who nearly crashes at his afternoon debut (on the FDA stage), dismays his fans by demanding their adherence to an intolerable liquid diet, then finally finds his niche as a bit player few shows can do without. Now, people trying to salvage a few more years of happy curtain calls with PI costars are looking at boosting ritonavir's billing from 100 mg at the matinee and evening shows to 200 mg at each performance. Three ICAAC studies reviewed this revamped script.

The one randomized study of the three involved 37 people taking lopinavir and amprenavir with 100 or 200 mg of ritonavir twice daily [abstract H-1078]. Everyone in the study had used at least two PIs and one NNRTI. Median baseline numbers included seven protease mutations, 207 $CD4^+$ cells/mm^3, and 4.7 log copies/mL (about 50,000 copies/mL). After 26 weeks, reported Gilles Raguin (Bichat Hospital, Paris), the median viral load had dropped 2.5 logs in the 200-mg ritonavir group and 1.4 logs in the 100-mg group ($P = 0.02$). Eleven people (61 percent) taking 200 mg twice daily and six (32 percent) taking 100 mg twice daily reached a viral load below 50 copies/mL ($P = 0.07$). $CD4^+$ counts rose about 120 cells/mm^3 in both groups.

The extra ritonavir did not compromise tolerability in this trial. Four in each study arm had to stop treatment. Seven (39 percent) in the 200-mg group and 10 (53 percent) in the 100-mg group had a grade 4 side effect. In a multivariate analysis, the extra ritonavir ($P = 0.007$) and fewer baseline protease mutations ($P = 0.02$) predicted virologic success. Baseline resistance phenotype did not predict success.

A larger, noncomparative study in people with shorter antiretroviral résumés and less advanced disease documented a reasonable six-month response to indinavir/ritonavir at a dose of 800/200 mg twice daily [abstract H-173]. Pompeyo Viciana and colleagues in Madrid and Barcelona gave doubly boosted indinavir plus two NRTIs to 105 people who had already tried an average of 2.2 PIs. Their baseline viral load averaged 4.3 logs (about 20,000 copies/mL) and their starting $CD4^+$ count 284 cells/mm^3.

After six months of indinavir/ritonavir, 41.9 percent had a viral load under 200 copies/mL in a noncompleter-equals-failure analysis. An on-treatment analysis showed that 54.4 percent had a sub-200 viral load. The average $CD4^+$ count climbed to 370 cells/mm^3. Baseline detection of mutations conferring resistance to indinavir and ritonavir (V82A and L90M) did not rule out a good response to the salvage regimen. But fewer people with the nelfinavir-linked D30N mutation responded.

Ritonavir-induced gastrointestinal (GI) problems proved the most frequent grade 3 or 4 toxicity, vexing 16 people (15 percent). In all, clinicians reported a toxicity of any grade in 38 people (36 percent).

A second noncomparative study in people with even better baseline barometers did not record a better response to the same dose of indinavir/ritonavir than did Viciana [abstract H-175]. David Parr from the University of Texas Medical Branch at Galveston, and coworkers in Georgia and Florida, treated 63 people with a mean $CD4^+$ count of 360 cells/mm^3 and a mean viral load of 3.85 logs (about 7,000 copies/mL). Forty-eight of them (76 percent) were taking their first failing single-PI regimen, while 15 (24 percent) were on their second PI or their first dual PI combo.

The initial study lasted 24 weeks, during which 16 people dropped out (seven because of toxicity). Of the 47 people who finished 24 weeks, 20 did not enroll in a 24-week extension because of the timing of the extension approval. Of the 27 who did continue, eight dropped out before week 48 (five because of toxicity).

In a 24-week noncompleter-equals-failure analysis, 35 people (56.5 percent) had a viral load under 400 copies/mL and 23 (37.1 percent) were under 50 copies/mL. In the 48-week analysis excluding the 20 people who could not re-enroll, 10 (23.3 percent) were under 400 copies/mL and nine (20.9 percent) under 50 copies/mL. A last-observation-carried-forward analysis charted mean $CD4^+$ gains of 96 cells/mm^3 at week 24 and 131 cells/mm^3 at week 48.

Not counting those unable to sign up for the 24-week extension, 24 people dropped out of the study at some point. Nine of the 24 (37.5 percent) quit because of side effects. But some of the other reasons for bowing out could reflect poor tolerance, such as withdrawn consent (five people) and loss to follow-up (three people). Eight of the toxicity-related dropouts (representing 13 percent of the original study group) involved GI intolerance, a possible consequence of the doubled ritonavir dose.

Clinicians considering the extra ritonavir boost have to weigh the virologic benefits recorded in studies like these against the risk of increased toxicity. And toxicity rates will surely vary depending on disease stage and other variables. In a case series at the Lipodystrophy Workshop a week before ICAAC, Düsseldorf clinician Stefan Mauss reported that eight of 11 people could not tolerate 200 mg of ritonavir twice daily with lopinavir (400 mg twice daily) and amprenavir (600 mg twice daily).[22] In an earlier study of lopinavir plus amprenavir with 100 mg of ritonavir twice daily, Mauss reported only one discontinuation among nine people because of GI toxicity.[23]

High lopinavir levels predict high lipids

Partly because of its potency against PI-resistant virus, and partly because it's the newest PI, lopinavir has become a rescue regimen favorite. Two cautionary studies at ICAAC found, though, that higher lopinavir levels correlate with hyperlipidemia in people taking a lopinavir/ritonavir salvage regimen.

Alice Tseng (Toronto General Hospital) measured fasting lipids in 21 people starting a lopinavir salvage combination [abstract H-1916]. After a median nine months of follow-up, the median total cholesterol rose from 4.46 to 5.60 mmol/L (172 to 217 mg/dL, $P < 0.001$) and median triglycerides from 2.22 to 4.71 mmol/L (197 to 417 mg/dL, $P < 0.09$). The median lopinavir trough concentration measured 4.13 µg/mL in people with high triglycerides and 2.64 µg/mL in people with low triglycerides ($P = 0.05$). Among people with high total cholesterol, the median lopinavir trough stood at 4.08 µg/mL versus 2.87 µg/mL in people with low total cholesterol, but that difference was not significant. Lopinavir peak concentrations did not correlate with hyperlipidemia in Tseng's analysis.

Studying 22 people taking lopinavir in salvage, Sergio Padilla (University Hospital, Elche, Spain) figured a mean lopinavir plasma level for each person based on three to nine troughs [abstract H-1915]. Percent increases in cholesterol and triglycerides from baseline to weeks 12 and 24 correlated positively with mean lopinavir levels ($r = 0.55$, $P = 0.008$, for triglycerides at week 12; $r = 0.55$, $P = 0.007$, for cholesterol at week 24). At week 48 cholesterol was significantly higher in people with higher lopinavir troughs (8.88 versus 5.67 mmol/L [343 versus 219 mg/dL], $P = 0.017$). Subcutaneous and adipose abdominal tissue measured by CT increased over 48 weeks. But fat changes did not correlate with lopinavir concentration.

How much PI experience a person has when starting lopinavir could make a difference. Among 70 of 100 people who took lopinavir/ritonavir for 204 weeks as part of their first antiretroviral regimen, 12 (17 percent) had cholesterol levels between 240 and 300 mg/dL and one (1 percent) had between 300 and 400 mg/dL [abstract H-165]. Robert Murphy (Northwestern University, Chicago) reported that nonfasting triglycerides stood between 400 and 750 mg/dL in 18 (26 percent) and above 750 mg/dL in four (6 percent). One of 100 study participants dropped out because of high lipids.

Amprenavariations

Drug concentrations (see above) and resistance are the yin and yang of rescue regimen planning. Two ICAAC studies shed more light on the yang.

A group of Spanish clinicians not affiliated with Virco found that Virco's VirtualPhenotype did better than standard phenotyping in picking more potent rescue regimens [abstract H-1079]. (The VirtualPhenotype matches a submitted isolate's

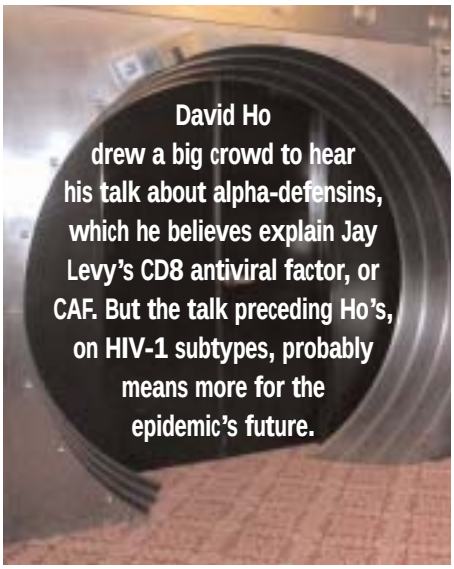
genotype with phenotypes of database viruses that have the same genotype.) This double-blind trial randomized 276 people from five outpatient clinics to have VirtualPhenotyping or standard phenotyping as a guide for their clinicians to pick new regimens. Most people (60 percent) had tried drugs from all three classes, and the average viral load hovered around 10,000 copies/mL.

Maria Jesus Perez-Elias reported that people in the Virtual arm got an average of 2.9 drugs rated "active," while those in the phenotyping arm got an average of 2.8. The 24-week missing-data-equal-failure analysis defined failure as a regimen switch because of virologic failure—but not because of intolerance. By that standard, the median viral load dropped 1.3 logs in the Virtual arm and 0.92 log in the phenotyping arm ($P = 0.008$). Respective proportions with a viral load below 400 copies/mL were 56.5 percent and 46.5 percent ($P = 0.01$).

At the 2002 Resistance Workshop, Neil Parkin plumbed ViroLogic's vast viral database to propose novel genotypic pathways promoting resistance to lopinavir.[24] At ICAAC he did the same favor for amprenavir. Analyzing more than 4,000 isolates, he found frequent discordance between genotypic resistance or sensitivity determined by four rule sets and phenotypic sensitivity or resistance determined with a conservative fold-change susceptibility cutoff of 2.5. For example, according to the ANRS algorithm, 15 percent of isolates called genotypically sensitive proved phenotypically resistant, and 7 percent called genotypically resistant proved phenotypically sensitive, for a total discordance score of 22 percent. All the rule sets yielded total discordance rates between 22 and 25 percent.

Because the genotypic rules relied on defined amprenavir mutations—V32I, I50V, I54L/M, and I84V—Parkin figured that genetic pathways not including amprenavir-selected mutations must contribute to slumping susceptibility. To scout out the mutational milestones on these shadowy pathways, he analyzed mutations at all protease positions that turned up in more than 1 percent of his samples. Then he used a univariate analysis to pick mutations that may contribute to reduced susceptibility to amprenavir, and he tested those mutations for resistance when combined with each other and with a second list of canonical protease mutations. This exercise yielded a suite of mutations and mutation sets that shave susceptibility to amprenavir:

1. 54A/S/T, 82F, 84C
2. 33F + 82A
3. 46I/L + 47V, 54V, 71L, 76V, or 82A



David Ho drew a big crowd to hear his talk about alpha-defensins, which he believes explain Jay Levy's CD8 antiviral factor, or CAF. But the talk preceding Ho's, on HIV-1 subtypes, probably means more for the epidemic's future.

If Parkin added the first set listed above to the mutations in current algorithms, total phenotypic-genotypic discordance dropped from 24.5 percent to 20.6 percent. If he then tossed in 33F + 82A, total discordance dwindled to 17.9 percent. Piling on the third set narrowed total discordance to 15.1 percent. Finally, Parkin verified the refurbished algorithm against a validation set of 1,634 resistant isolates not included in the set used to track down the newly implicated mutations. Along the way to these findings, he also showed that resistance conferred by amprenavir's signature mutation, I50V, can be reversed by the N88S substitution.

FEARFUL SYMMETRY

During idle moments preceding each session's start, ICAACers got stared down by the looming meeting logo, a tiger's face selected, perhaps, to advertise San Diego's zoo. But the balanced harmonies of that graphic also put one in mind of William Blake's tiger, prowling night's forests, never worrying what immortal hand or eye could frame its fearful symmetry.[25]

Retroviral researchers of every stripe have now stalked HIV through dusky forests for 20 years. And some did frame fearful symmetries—X4 and R5 viruses, unraveling error-prone RNA strands, and life-saving two-target therapies come to mind. But the talk of HIV research as this year's ICAAC unfolded was whether Linqi Zhang and David Ho (Aaron Diamond AIDS Research Center, New York) had managed to frame another symmetry by completing a coup with CAF—Jay Levy's long-since discovered, but never defined, CD8 antiviral factor. As Fate's immortal hand would have it, ICAAC organizers had already slated Ho to talk during a pathogenesis plenary. And by the time he took the stage, everyone knew the "Host factors that suppress HIV replication" in his talk's title were alpha-defensins [presentation 1192].

Never mind that few—if any—attendees had ever heard of these pint-sized proteins before Zhang and Ho's paper went online.[26] Many could appreciate the neat symmetries here. Levy published his CAF discovery in *Science* in 1986,[7] but diligent work in his lab never managed to nab the culprit molecule. Over the years Levy emerged as an outspoken critic of Ho's eradication essays,[27] not to mention his hit-hard-hit-early tenet.[28] Now, 16 years after CAF's first sighting, Zhang and Ho's paper, again in *Science*, claims their findings "show that alpha-defensins-1, -2, and -3 collectively account for the anti-HIV-1 activity of CAF that is not attributable to beta-chemokines."[26]

Alpha-defensins, which Zhang identified with a novel gene chip, turned up in $CD8^+$ cells from three of three nonprogressors, none of four rapid progressors, and 11 of 15 volunteers without HIV infection. Zhang showed that antibodies against alpha-defensins eliminate CAF activity, and that adding synthetic alpha-defensins to HIV-infected cells inhibits HIV replication.

Although the discoverer of alpha-defensins called this work "very convincing,"[8] not everyone buys the conclusion that they account for the tiger's share of CAF's anti-HIV action. The study population was small; the antiviral activity weak; and no one could explain how alpha-defensins, which breach the walls of noxious bacteria, also bring down HIV. (For more detailed reviews of Zhang's study, see references 8 and 29.)

But there's a bigger question about this research: What does it mean for the millions of people with HIV who are not long-term nonprogressors? The most optimistic answer is that—if Zhang and Ho are right about alpha-defensins'

antiviral role—this work could lead to novel antiviral strategies. But, appropriately, Ho himself downplayed that possibility in press interviews. Whether synthetic alpha-defensins could be turned into a tolerable drug, and—if they can—whether they would stop HIV in humans without unhinging healthful doings, remain weighty riddles.

No. The talk that preceded Ho's framed a symmetry that means more to people destined to become long-, short-, or mid-term progressors. Back when CAF came to light in Levy's lab, virologists thought about two types of HIV-1—the type found in North America, and the type found in Africa, explained Thomas Quinn of Johns Hopkins University [presentation 1191]. A scant six years later, viral orthographers had named five subtypes—or clades—of the retrovirus, A through E.[30] That was only the beginning.

Now we are up to subtype K, and there is talk of L. But wait. It gets more complicated. Some of the original subtype designations turned out to be wrong. Today's subtype E, for example, really represents a circulating recombinant form (CRF) of A and some older E. Subtype I actually denotes a CRF that recombines four parental strains. So far researchers have tallied 14 CRFs, and they haven't stopped to catch their breath.

Why is this important?

There is a one-word answer: vaccines. No one knows whether a worthwhile vaccine must be effective across clades and also across CRFs. When Harvard's Bruce Walker described a case of HIV-1 superinfection at the XIV International AIDS Conference,[31] what most troubled experts was that the superinfected person's immune system recognized the new virus and mounted a response. But this man's strong and broad T-cell responses did not protect him from a second virus of the same subtype (B) that differed from his first virus by only 12 percent at the protein sequence level. As Duke University's Kent Weinhold told *IAVI Report*, "These data challenge our notions that magnitude and breadth translate into protection."[32]

IAVI Report goes on to explain why this case of superinfection may not spell doom for vaccine research. The index case had HIV to begin with, and even minimally compromised immunity could make him more susceptible to reinfection than a freshly vaccinated, uninfected person. His immune response to the new virus was cell based, and no one expects a CTL-based vaccine to block infection. But, to tell the truth, everyone would be happier if this man's immune system had fought off the new virus.

As Quinn noted, leaders in this field disagree when estimating the impact of viral diversity on vaccine development. Andrew McMichael (Oxford) thinks vaccine developers have to trek from region to region, sample the locally prevalent virus, then use it to brew a local vaccine. Bette Korber (Los Alamos National Laboratory) believes they must time-travel all the way back to the parental HIV-1—via computer calculations—if they want to make a vaccine that works. Quinn himself proposed that a vaccine derived from subtypes A, B, C, and D, plus CRF01 and CRF02, which account for 85 percent of worldwide infections, holds the most promise.

So far, of course, no one seems close to a single-subtype vaccine.

Those fearfully symmetric correlates of protection, which a potent vaccine would mimic, remain unframed. ■

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

References and Notes

1. Garrett L. AIDS seen as threat to world: experts say five countries may soon be decimated. *Newsday* October 15, 2002. http://ww2.aegis.org/news/newsday/2002/ND021001.html.
2. Gottlieb MS, Schroff R, Schanker HM, et al. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. *N Engl J Med* 1981;305:1425-1431.
3. Masur H, Michelis MA, Greene JB, et al. An outbreak of community-acquired *Pneumocystis carinii* pneumonia: initial manifestation of cellular immune dysfunction. *N Engl J Med* 1981;305:1431-1438.
4. Siegal FP, Lopez C, Hammer GS, et al. Severe acquired immunodeficiency in male homosexuals, manifested by chronic perianal ulcerative herpes simplex lesions. *N Engl J Med* 1981;305:1439-1444.
5. Centers for Disease Control. West Nile virus update: current case count. October 31, 2002. http://www.cdc.gov/od/oc/media/wncount.htm.
6. Centers for Disease Control. Acquired immunodeficiency syndrome (AIDS) weekly surveillance report—United States. December 22, 1983. http://www.cdc.gov/hiv/stats/surveillance83.pdf.
7. Walker CM, Moody DJ, Stites DP, Levy JA. $CD8^+$ lymphocytes can control HIV infection in vitro by suppressing virus replication. *Science* 1986;234:1563-1566.
8. Cohen J. Mystery anti-HIV factor unmasked? *Science* 2002;297:2188. Jon Cohen's article reviewing the Aaron Diamond study nominating alpha-defensins as the main component of $CD8^+$ antiviral factor (CAF) cites Robert Gallo's argument that $CD8^+$ cells secrete numerous antiviral "factors" and that no "single mysterious, undiscovered" factor exists. "We don't use the word 'CAF,'" Gallo told Cohen. "Throw it out."
9. Hogg RS, Yip B, Chan KJ, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA* 2001;286:2568–2577.
10. Sterling TR, Chaisson RE, Keruly J, Moore RD. When to initiate highly active antiretroviral therapy (HAART): HIV disease progression according to $CD4^+$ level at initiation of therapy among persons with durable virologic suppression. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle. Abstract 469.
11. Egger M, May M, Chêne G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 2002;360:119-129. http://www.thelancet.com/journal/vol360/iss9327/full/llan.360.9327.original_research.21718.1.
12. James JS. HIV medicine after Barcelona Conference: Interview with Howard Grossman, M.D. *AIDS Treatment News* 2002;383. September 6. http://www.thebody.com/atn/383/interview.html
13. Bartlett JA, DeMasi R, Quinn J, et al. Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1-infected adults. *AIDS* 2001;15:1369-1377.
14. Kostrikis LG, Touloumi G, Karanicolas R, et al. Quantitation of human immunodeficiency virus type 1 DNA forms with the second template switch in peripheral blood cells predicts disease progression independently of plasma RNA load. *J Virol* 2002;76:10099-10108.
15. Rouzioux C. Early HIV-1 DNA level predicts disease progression and death independently of HIV-RNA level and CD4 cell count. 1st IAS Conference on HIV Pathogenesis and Treatment. July 8-11, 2001. Buenos Aires. Abstract 23.
16. Schacker TW, Nguyen PL, Beilman GJ, et al. Collagen deposition in HIV-1 infected lymphatic tissues and T cell homeostasis. *J Clin Invest* 2002;110:1133-1139. http://www.jci.org/cgi/content/full/110/8/1133.
17. Krolewiecki AJ, Zala C, Gun A, et al. Treatment discontinuation in patients who started antiretroviral therapy following the 1996 IAS-USA recommendations: a prospective randomized trial. XIV International AIDS Conference. July 7-12, 2002. Barcelona. Abstract ThOrB1440.
18. Parish MA, Tarwater P, Lu M, et al. Prolonged treatment interruption after immunologic response to HAART. XIV International AIDS Conference. July 7-12, 2002. Barcelona. Abstract ThOrB1439.
19. Kuritzkes D. Beginning antiretroviral therapy: a world of options. XIV International AIDS Conference. July 7-12, 2002. Barcelona. Presentation TuOrB157.
20. Clotet B, Lazzarin A, Cooper D, et al. Enfuvirtide (T-20) in combination with an optimized background (OB) regimen vs. OB alone in patients with prior experience or resistance to each of the three classes of approved antiretrovirals in Europe and Australia. XIV International AIDS Conference. July 7-12, 2002. Barcelona. Abstract LbOr19A.
21. Henry K, Lalezari J, O'Hearn M, et al. Enfuvirtide (T-20) in combination with an optimized background (OB) regimen vs. OB alone in patients with prior experience or resistance to each of the three classes of approved antiretrovirals in North America and Brazil. XIV International AIDS Conference. July 7-12, 2002. Barcelona. Abstract LbOr19B.
22. Mauss S, Scholten S, Wolf E, et al. High rate of gastrointestinal side effects in patients treated with amprenavir, lopinavir and ritonavir (200 mg twice daily). 4th International Workshop on Adverse Drug Reactions and Lipodystrophy. September 22-25, 2002. San Diego. Abstract 93.
23. Mauss S, Schmutz G, Kuschak D. Unfavourable interaction of amprenavir and lopinavir in combination with ritonavir? *AIDS* 2002;16:296-297.
24. Parkin NT, Chappey C, Petropoulos CJ. Mutations in HIV-1 protease associated with resistance to amprenavir contribute towards phenotypic resistance to lopinavir. *Antiviral Therapy* 2002;7(suppl 1):S29. Abstract 24. For discussion, see Mascolini M. Digging deeper at the Resistance Workshop. International AIDS Society. August 2002. http://www.ias.se/article/show.asp?article=1591.
25. Tiger! Tiger! burning bright
In the forests of the night,
What immortal hand or eye
Could frame thy fearful symmetry?
26. Zhang L, Yu W, He T, et al. Contribution of alpha-defensin-1, -2, and -3 to the anti-HIV-1 activity of CD8 antiviral factor. *Science* 2002; 298:995-1000.
27. Levy J. Track A. Basic science. Rapporteur session. 12th World AIDS Conference. June 28-July 3, 1998. Geneva.
28. Levy JA. Caution: should we be treating HIV infection early? *Lancet* 1998; 352:982-983. http://www.thelancet.com/journal/vol352/iss9132/full/llan.352.9132.editorial_and_review.6047.1.
29. O'Brien WA. Identity of soluble CD8 antiviral factor (CAF) is revealed. Medscape HIV/AIDS. September 29, 2002. http://www.medscape.com/viewarticle/442254.
30 Myers G, MacInnes K, Korber B. The emergence of simian/human immunodeficiency viruses. *AIDS Res Hum Retroviruses* 1992;8:373-386.
31. Walker B. Harnessing the immune system to fight HIV infection. XIV International AIDS Conference. July 7-12, 2002. Barcelona. Presentation WeOrA197.
32. Kahn P. Superinfection: what does it mean for vaccines? *IAVI Report* 2002:6(4):3-4. http://aidscience.org/articles/iavi008.asp.

Jamila Aboobaker

Vanity Fair readers have every month since 1993 enjoyed *The Proust Questionnaire*, a series of questions posed to celebrities and other famous subjects. In May 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 Jamila Aboobaker, who is Head of the Department of Dermatology at the Nelson R. Mandela School of Medicine, University of Natal in Durban, South Africa.

What proverb, colloquial expression, or quote best describes how you view the world and yourself in it?
Perseverance and tenacity achieves success.

What activities, avocations, or hobbies interest you? Do you have a hidden talent?
Reading, listening to classical music, aerobic exercises and long walks.

If you could live anywhere in the world, where would it be?
South Africa. I have traveled through many countries and find that South Africa is one of the most beautiful countries I have seen. It has a very democratic and well meaning government with the best constitution in the world. However the government is grappling with service delivery because of the poor financial status (due to globalization) and the lack of skilled manpower.

Who are your mentors or real life heroes?
My father (now deceased) emphasized over and over again the importance of education as a means of liberation and independence. Dr Nelson Mandela, the man of the millennium and Nobel Laureate is a real life hero, for all his achievements, forbearance, forgiveness and willingness to make this a better world for all who inhabit it.

With what historical figure do you most identify?
Florence Nightingale—I love and care for the sick as she did. I have spent all my working life in the public sector.

Who are your favorite authors, painters, and/or composers?
Author: Upton Sinclair; Painter: Van Gogh; Composers/Musicians: Mozart, Beethoven, Chopin, and Tchaikovsky.

If you could have chosen to live during any time period in human history, which would it be?
The present. Man has achieved so much technologically and scientifically. Man now has to improve on humanity.

If you did not have the option of becoming a physician, what would you have likely become given the opportunity?
I enjoy my work and am happy doing what I do, that is, teach and help the ill.

In your opinion, what are the greatest achievements and failures of humanity?
Man's greatest achievements have been in science and technology. Man's failures are the lack of humanity and the making of the atom bomb. Also the United Nations has failed miserably in keeping world peace. There are pockets of war going on in many parts of the world.

What is your prediction as to the future of our planet one full decade from present day?
If the warmongers are not curbed the world will be destroyed. We need another Messiah. Subsaharan Africa is going through the worst epidemic of all times—the HIV-AIDS catastrophe. ■

SAY ANYTHING

We say that prevention ... is called chastity.
Monsignor Javier Lozano Barragan, President of the Pontifical Council for Health Workers, reiterating on November 6, 2002, the Vatican's stance that abstinence is the only way to prevent the spread of HIV/AIDS, as reported by the Associated Press. Barragan went on to express the Catholic Church's criticism of viewing sex as a recreational act separate from procreation.

Public and private partners in Ghana are showing a commitment to a new way of doing business. The Global Fund will give them the resources to take effective programs to scale and to ensure comprehensive responses to diseases of poverty.
Richard Feachem, Executive Director of the Global Fund to Fight AIDS, Tuberculosis, and Malaria in a November 22, 2002, press release announcing the Global Fund's first ever grant agreement: a total of US$6.5 million for a variety of projects in Ghana that will treat 2,000 people living with AIDS and 20,000 people living with tuberculosis. Another agreement that would have sent US$12 million to Tanzania, and was to be the nearly one-year-old Global Fund's first grant, was put on hold earlier the same week after the Tanzanian government insisted that the funding would have to be administered through its finance ministry, rather than the ministry of health, as the Global Fund requires. According to the press release, the Global Fund is negotiating agreements with 39 other countries that were approved for funding in its first proposal round.

[N]owhere has [UN Secretary General Kofi Annan's] leadership and foresight been more important than in marshalling the international community against the biggest problem that we have on the face of the earth today, and that's the HIV / AIDS pandemic.
US Secretary of State Colin L. Powell speaking November 12, 2002, at the United Nations Association of the USA Visionaries Awards Dinner in Washington, DC. The dinner was the setting of a tribute to Annan.

If George Bush spent more time and money on mobilizing Weapons of Mass Salvation (WMS) in addition to combating Weapons of Mass Destruction (WMD), we might actually get somewhere in making this planet a safer and more hospitable home.
Jeffrey Sachs, director of the Earth Institute at Columbia University (New York) in a guest opinion piece for The Economist. *The article called on the United States to make a higher priority of fighting poverty and disease abroad, and argued the United Nations and its constituent agencies are the best vehicles through which to wage such a fight.*

The AIDS epidemic claimed more than 3 million lives in 2002, and an estimated 5 million people acquired the human immunodeficiency virus (HIV) in 2002 — bringing to 42 million the number of people globally living with the virus.
The first sentence of AIDS Epidemic Update, *a biannual report of the Joint United Nations Program on HIV/AIDS (UNAIDS) and the World Health Organization (WHO). The report was released November 26, 2002, in advance of World AIDS Day 2002.*

The message is clear — give us your money to fight AIDS, Mr. Gates, but don't raise any uncomfortable questions.
From a November 11, 2002, Times of India *editorial, one of several from Indian newspapers that criticized the Indian government, and Health Minister Shatrughan Sinha, in particular, for their response to the country's AIDS epidemic. Sinha accused Bill Gates and the US Ambassador to India of unjustifiably "spreading panic" about the epidemic, even while accepting a US$100 million donation for fighting the disease from the Bill & Melinda Gates Foundation. Recent reports have predicted that India could have as many as 25 million people living with AIDS by 2010; the Indian government has stated that such estimates are serious overstatements.*

African societies' capacity to resist famine is fast eroding. Hunger and disease have begun reinforcing each other. As daunting as the prospect is, we will have to fight them together, or we will succeed against neither.
Alex de Waal, director of Justice Africa and an adviser to the United Nations Economic Commission for Africa and UNICEF, in a November 19, 2002, New York Times *guest editorial. De Waal described how AIDS exacerbates famine because it disproportionately affects working age adults who could otherwise provide food; prevents parents from passing on famine-coping skills and acquired economic assets to their children; and increases a community's total nutritional requirements because HIV-infected people need more calories and protein to fight off the progression of AIDS.*