March 2004 VOL. 10, NO. 3

IAPAC

MONTHLY

Why people with HIV still DIE — and why they don't have to...

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Volume 10, Number 3

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Mark Mascolini

Thousands of people with HIV in developed countries die every year despite access to antiretrovirals. Most of them, research shows, are not people who used up treatment options and now battle a highly drug-resistant virus. Can the deaths of all those with drug-susceptible virus be prevented? For many of them, the answer appears to be yes.

DEPARTMENTS

IAPAC Monthly (ISSN 1545-1089) 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.

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Reauthorizing the Ryan White CARE Act

José M. Zuniga

First diagnosed in 1981, a year during which many current medical students were born, the human immunodeficiency virus (HIV) has accompanied us down a long and frustrating road. All of our hurdles taken into account, the daunting scientific battle that we face in coping with this disease continues to be eclipsed by the social and political tug-of-war that is being fought globally to ensure equitable and appropriate care for those living with the virus. While the images may differ, this lamentable state of affairs continues to plague resource-rich and -poor countries alike.

In the United States, 2004-2005 marks a critical period in this history due to the third round of negotiations for reauthorization of the government's landmark legislation dealing specifically with HIV/AIDS care and treatment. Enacted in 1990, the Ryan White Comprehensive AIDS Resources Emergency (CARE) Act, which provides the lion's share of financial support that states, cities, and institutions need to combat HIV/AIDS in the United States, comes up for reauthorization by the US Congress later this year.

With the lives and welfare of millions of Americans at issue—to say nothing of the ripple effect that US action on HIV has traditionally had internationally—the clinical care community's efforts to ensure appropriate reauthorization of (and funding for) the Ryan White CARE Act will take on unparalleled significance this year. The act, which must be reauthorized no later than every five years, requires collective maintenance and refurbishing in this instance as never before.

More than 20 years into our struggle, and with no cure or viable vaccine for HIV on the immediate horizon, it is incredibly important that care providers walk hand in hand with the patient community to ensure that the challenges inherent in both living with and treating this infection and its myriad complications are duly reflected in the act that is reauthorized. With that in mind, the International Association of Physicians in AIDS Care (IAPAC) recently joined forces with domestic US organizations to launch a multi-pronged Ryan White CARE Act reauthorization campaign.

Beginning with an inaugural community summit held last month during the 11th Conference on Retroviruses and Opportunistic Infections (CROI), IAPAC, the HIV Medicine Association (HIVMA), American Academy of HIV Medicine (AAHIVM), AIDS Institute, Association of Nurses in AIDS Care (ANAC), National Association of People with AIDS (NAPWA), and Physician Assistant AIDS Network (PAAN) initiated what will be a one-year-plus campaign to present the voices of care providers and patients to US policy makers and their constituents.

IAPAC and our partner institutions have taken an unprecedented step to put forward a harmonized message around current needs and priorities in the fight against HIV/AIDS in the United States. More will be forthcoming in this regard on a regular basis over the course of 2004, and into early 2005.

IAPAC is intent on playing a strong facilitating role in channeling the voices of our association's 6,900-plus US physician members, whom I encourage to pay close attention to both the IAPAC Web site at www.iapac.org and the *IAPAC Monthly* for important updates and news about opportunities to become involved at the federal, state, and local levels in activities that will be planned for the upcoming year.

These opportunities, and efforts for which we sincerely request active participation, will range from briefings before the US Congress, to planned, clinical day-visits for political representatives, to expert testimony regarding HIV care. All of these activities that IAPAC will unfold, both independently and in harmony with partner organizations, intend to present to legislators the impressions and requests of those who are tasked with the responsibility of ensuring wellness for patients with HIV/AIDS: You, the care and support providers.

While it is always on my mind as the chief executive officer of an association representing the interests and concerns of care providers globally who are at the side of those living with HIV/AIDS, this is a particularly poignant time for me to reiterate IAPAC's sincerest appreciation for the leadership of our members across the globe, and for your continued demand that IAPAC be a vehicle to bring your clinical and social expertise to the table. We have no greater satisfaction than to assist in making sure that our members are well equipped to deliver the best available care and treatment for their patients and are supported in achieving continued safety and comfort both within the clinical setting and in professional life.

From the outset of the Ryan White CARE Act reauthorization campaign, I want to thank you in advance for the leadership that I know many of you may be counted on to provide. And, I reiterate to you our standing request that you continue to submit to us your concerns, your requests, and your statements of need. ■

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

Resistance: What are the implications for treatment?

Keith Alcorn

Although drug resistance may linger for months or even years when individuals become infected with drug-resistant HIV, evidence from a large European study does not suggest that these individuals have a poorer response to first-line antiretroviral therapy, according to findings presented at last month's 11th Conference on Retroviruses and Opportunistic Infections (CROI) in San Francisco.

A range of studies from North America and Europe presented at the conference have shown that resistance mutations are far more persistent than previously assumed in individuals followed after acquisition of antiretroviral drug-resistant HIV. In particular, resistance to nonnucleoside reverse transcriptase inhibitors (NNRTIs) can persist for at least two years after infection, researchers reported.

Susan Little (University of California, San Diego) reported on 12 individuals infected with drug-resistant virus, identified an average of 56 days after exposure to HIV. Ten had acquired virus with genotypic evidence of NNRTI resistance, five had protease inhibitor- (PI) resistant virus, and five had nucleoside reverse transcriptase inhibitor- (NRTI) resistant virus (two had multidrug-resistant virus resistant to agents in all three drug classes, and three had virus resistant to at least one drug in two drug classes).

Only one patient with NNRTI-resistant virus experienced any increase in drug susceptibility during a median follow-up period of 310 days, and the mean time to the emergence of any variants without the acquired NNRTI mutation (wild type) was 375 days. No PI mutations disappeared during the follow-up period, while viruses with NRTI mutations did not begin to be replaced by wild-type viruses until an average follow-up of one year had elapsed. The M184V mutation associated with lamivudine (3TC) treatment was identified in two patients, and reverted to wild type after 181 days and 327 days respectively. One patient totally reverted to wild-type virus, after follow-up of 2.8 years.

Multidrug resistance has been associated with low replication capacity, and hence less harm to CD4 counts, in other studies, but in this sample replication capacity was high, leading Little to suggest that drug-resistant variants with higher replication capacity will tend to be favored for transmission. She also warned that persistence may amplify the transmission of drug resistant virus.

Pat Cane (Antiviral Susceptibility Unit, Health Protection Agency, London) reported that mutations associated with zidovudine (ZDV) and NNRTI resistance persisted for up to 33 months in patients identified through a United Kingdom study of newly infected individuals. Participants were followed prospectively after identification and tested on a regular basis to identify patterns of genotypic resistance.

Eighteen patients with drug resistance were identified in this study. The M41L mutation associated with ZDV treatment was found in five, and persisted to the last sample in the study, taken between seven and 33 months post-seroconversion. Six patients had mutations at codon 215, also associated with ZDV treatment. A variety of amino acid patterns were noted at this codon; in four cases the amino acid pattern remained stable, while in two cases a switch from T215Y to T215C was observed.

Nonnucleoside reverse transcriptase inhibitor resistance was seen in five patients, three of whom had acquired multidrug resistant viruses. Two patients experienced loss of NNRTI resistance after 23 and 25 months, but those with multidrug resistance exhibited unchanged resistance patterns at last follow-up (17, 24, and 18 months after seroconversion). These patients also had PI resistance mutations that remained unchanged throughout the follow-up period. ■

Editor's Note: *Reprinted with permission from www.aidsmap.com (first e-published February 12, 2004).*

New warning issued about NVP liver toxicities

Michael Carter

Boehringer Ingelheim issued important new safety information in February 2004 about its nonnucleoside reverse transcriptase inhibitor (NNRTI). The information specifically relates to potentially fatal liver toxicities associated with nevirapine (NVP).

Safety information contained in packets of the drug will now caution that women with CD4 counts above 250 cells/mm^3, including pregnant women, who are taking NVP for chronic HIV infection, have a 12-fold greater risk of serious liver side effects, and that these have sometimes been fatal.

Liver events present the greatest risk of fatality if they occur in the first six weeks of NVP treatment, and are often associated with a rash. However, the risk continues after this time and Boehringer Ingelheim is cautioning physicians to closely monitor patients for the first 18 weeks of NVP therapy. Even when NVP treatment is discontinued, the manufacturer is warning that in some instances hepatic injury has continued to progress.

Any patient taking NVP can experience hepatic toxicities. Thus, some physicians recommend that NVP-treated patients should be monitored more often than once a month. In particular, it is recommended that liver function be monitored before initiating NVP treatment, at the time of NVP dose escalation, and two weeks later. It is also stressed that any patient on NVP who develops a rash should have a liver function test immediately, particularly during the first 18 weeks of therapy with the drug.

Editor's Note: *Reprinted with permission from www.aidsmap.com (first e-published January 30, 2004).*

Abbott announces RTV price concessions

Keith Alcorn

Abbott Laboratories announced a series of concessions February 4, 2004, meant to defuse two months' worth of fierce criticism over the company's decision to quadruple the price of its protease inhibitor, ritonavir (RTV), in the United States. Among these concessions, while Abbott Laboratories had previously promised to freeze RTV's price at the old level for state AIDS Drug Assistance Programs (ADAPs) until June 2005, the company has now promised to freeze the price at this level permanently.

Despite the concessions, anger among some US physicians appears to be growing. At a February 11, 2004, press conference called by the AIDS Treatment Activists Coalition and the Organization of HIV Health Care Providers, Ben Young (Rose Medical Center, Denver) told reporters that more than 200 anti-HIV drug prescribers in the United States had signed on to protest Abbott Laboratories' actions by boycotting the company's products and promotional activities.

Editor's Note: *Reprinted and adapted with permission from www.aidsmap.com (first e-published February 11, 2004).*

Editor's Note: *Following is an abbreviated version of a February 4, 2004, letter jointly issued by John Leonard, Abbott Laboratories' Vice President for Global Pharmaceutical Development, and Jesus Leal, Abbott Laboratories' Vice President and General Manager-Abbott Virology. The complete, unedited version of this letter may be obtained by calling (847) 935-4100.*

Dear HIV-treating clinician:

We have heard concerns from a number of sources regarding the recent re-pricing of Norvir (ritonavir). Over the past eight weeks, Abbott representatives have met with hundreds of members of the HIV community, including HIV care providers; patients; advocates; private and public payers; and government officials. We have listened carefully to the concerns you have expressed and have taken your concerns to heart. We recognize that our communication regarding this re-pricing was not well handled. Please accept our apology.

Following is a summary of the issues that you have identified and the actions we have developed to address your specific concerns:

Patient access

- As you know, we have committed to freeze the price of Norvir soft gelatin capsules at its former price for AIDS Drug Assistance Programs (ADAPs) through June 2005. Abbott now commits to freeze the price to ADAPs for Norvir soft gelatin capsules permanently.

- Abbott also pledges to keep Norvir soft gelatin capsules on the market permanently, ensuring that public programs, such as ADAP and Medicaid, continue to have this as a low-cost alternative.
- Abbott will continue to provide Norvir free to any ADAP-eligible patient on a waiting list.
- Abbott commits to making a 30-count bottle available to patients as soon as possible, in addition to the 120-count bottle available today. The 30-count bottle will also make dispensing more convenient.
- Abbott expanded its Patient Assistance Program (PAP) to ensure that any patient without drug coverage can get Norvir free, regardless of their financial status.
- In addition, Abbott will provide Norvir free to anyone who has exceeded his or her coverage maximum for annual prescription drug benefits.
- These expanded benefits will be in place permanently.

Future HIV drug development

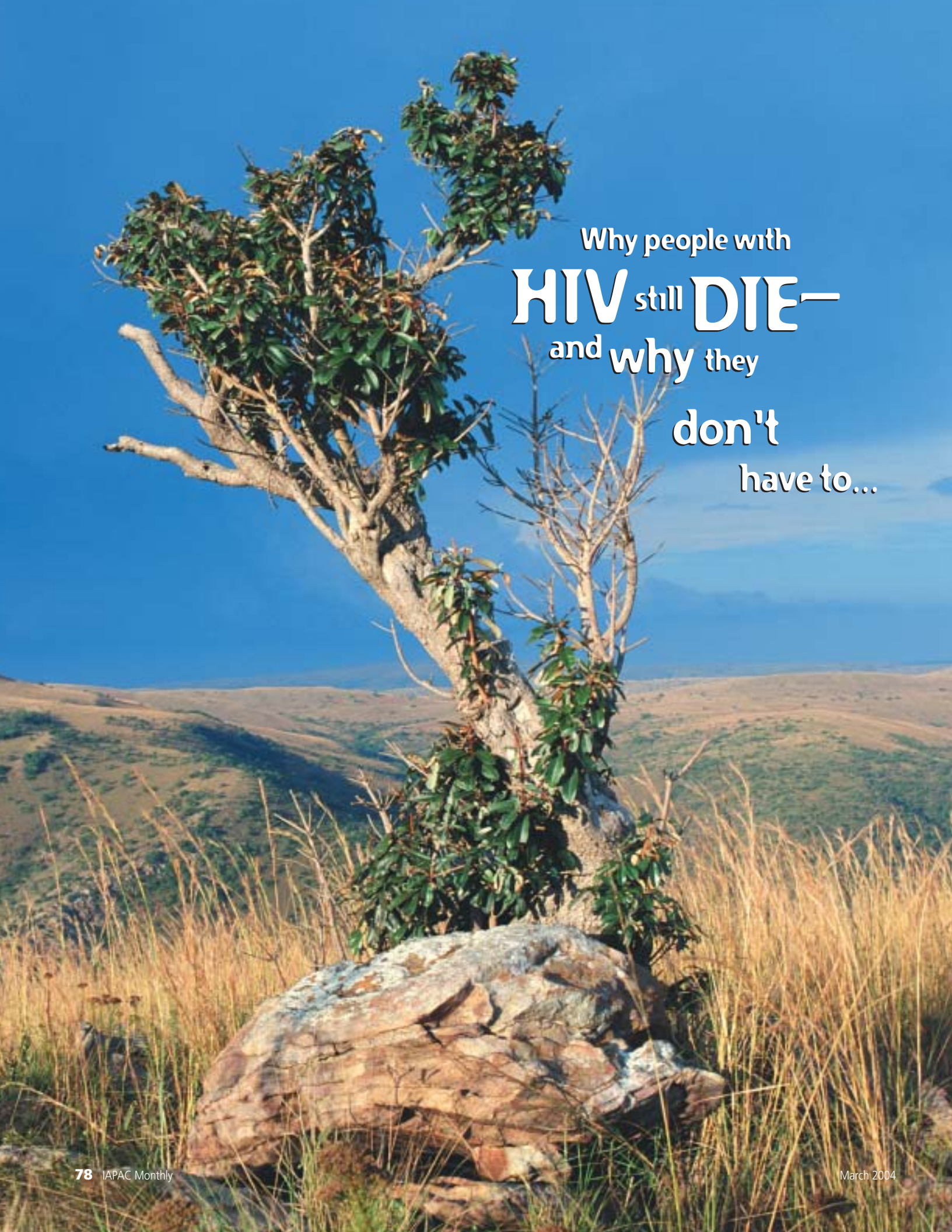
- To address the potential impact on the cost of future drug development, Abbott will provide Norvir 100 mg soft gelatin capsules for use in clinical development trials with new chemical entities, at the former price of US$1.71—or less.
- Abbott also pledges to approach companies that have salvage compounds in development to explore options that will ensure that these therapies are affordable to patients upon market availability.

Drug pricing

Norvir plays a central role in the treatment of HIV. While the number of patients receiving Norvir as a boosting agent has grown over time, there has been a steady decline in sales due to the significant reduction in dose, with the majority of patients now taking 100 mg daily, as opposed to the initial 1,200 mg daily. At the same time, the value of Norvir to patients with HIV has increased significantly. Abbott has taken this re-pricing step with Norvir in order to come to terms with these economic realities, while others have addressed this through the premium pricing of their new drugs.

Even at the new price, Norvir, at its most commonly used form of 100 mg, is most often the lowest cost component of a PI-based regimen, and represents a fraction, typically one-third to one-fourth, of the daily cost of many typical HIV therapies.

Ultimately, the re-pricing of Norvir, coupled with the additional steps we have outlined, ensure that we can continue to work together to make advances in the treatment of HIV/AIDS and to serve the best interests of patients. ■



Why people with HIV still DIE— and why they don't have to...

Mark Mascolini

Clichés cling to medical literature as insistently as burrs to burlap. But no cliché has clung to HIV literature as tenaciously as one that arose circa 1997, when AIDS mortality began its plunge in North America, Western Europe, and Australia. Every other published article and every third meeting abstract—it sometimes seems—starts with some version of this trusty formula:

The advent of potent antiretroviral therapy has led to dramatic declines in deaths from AIDS. However . . .

The study's title always gives away the next sentence: "However, treatment-induced toxicities have grown more worrisome as people live longer," or "However, failure to eradicate HIV has increased the challenge to develop adjunctive immune-based therapies," or "However, the prospect of lifelong therapy has prompted intense study of treatment interruptions."

In countries with good access to antiretrovirals, people still die from AIDS if it is diagnosed too late, if they have been unable to take antiretrovirals (for example, because of intolerable side effects), or if they have a condition that antiretrovirals may not improve, such as progressive multifocal leukoencephalopathy. People with HIV infection who respond well to antiretrovirals may die from other causes such as liver disease, heart disease, cancer, or accidental deaths. The risk of death from many of these conditions can be reduced by behavior change. This article describes recent research on HIV-related mortality in developed countries, relevant case reports, and steps clinicians might take to lower the death rate among people with HIV infection.

So far, apparently, no one has penned an equally defensible corollary to this ubiquitous bromide: "However, an awful lot of people still die with HIV." One need not even reference the thousands who die daily around the globe because they cannot get antiretrovirals. This article does not address those untreated throngs, or people in the United States, for example, who die killing time on an AIDS Drug Assistance Program (ADAP) waiting list.[1]

Instead, this *IAPAC Monthly* article considers the thousands who can and usually do get potent antiretrovirals but die anyway. Their numbers may be dwindling, but they are far from small. The US Centers for Disease Control and Prevention (CDC) estimates that 50,610 people with HIV died in the United States in 1995, the year before potent combinations turned the tide.[2] By 1998 better treatment had more than halved that number, but 19,005 people with HIV still died in the United States.[3] The tally continued to drop in the 21st century but stood at a still dismaying 16,371 in 2002.[3]

EuroSIDA analyzed all 1,826 deaths in the pan-European cohort from 1994 through 2001.[4] The largest proportion, 43.8 percent, died in the pre-HAART years 1994 and 1995, but one third died in 1996-1997, and nearly one quarter died in 1998-2001. At the Owen Clinic of the University of California, San Diego, a study of nearly 5,000 patients who sought care for HIV showed a drop in the death rate starting in 1995, but then an upswing among those who came to the clinic after 1998.[5] A survey of almost 3,000 people enrolled in five US antiretroviral trials between December 1996 and December 2001 plotted a dogged doubling of the death rate every 12 months, from 3.9 percent after one year of follow-up, to 7.9 percent after two, and to 13.1 percent after three.[6]

Should so many people with HIV still be dying? Can all their deaths be ascribed to HIV's remorseless immune carnage, its maddening knack to morph toward resistance? No, a growing stack of careful studies shows. E-mail surveys and interviews with more than two dozen HIV clinicians and researchers across the United States, Europe, and elsewhere confirm that other forces are at play. A few examples:

- At a major teaching hospital in Texas, *Pneumocystis carinii* pneumonia (PCP) accounted for an equivalent proportion of deaths before HAART in 1995 (21 of 112, or 19 percent) and well into the HAART era in 1999-2000 (15 of 88, or 17 percent, $P = 0.76$).[7]
- An analysis of 66 deaths in France's Aquitaine cohort in 1998 and 1999 blamed 11 of them (17 percent) on treatment-induced toxicities.[8]
- In British Columbia, where access to antiretrovirals is universal and free, only pretreatment CD4 count and intermittent therapy predicted death in a study of 1,282 people beginning their first antiretrovirals between August 1996 and December 1999.[9]

Even the most skilled HIV clinicians working in an ideal healthcare system cannot prevent all deaths like these. But surely different decisions in such cases—by physicians or by infected people—would have saved lives. And certainly treatment by clinicians not skilled in HIV medicine has ruined many a person's shot at successful therapy—a fact documented before[10,11] and after[12] potent therapies arrived.

Through a review of the literature and input from top HIV treaters and researchers, this article will try to: (1) itemize the emerging and persisting causes of death in HIV-infected people with access to good treatment, and (2) pinpoint those causes that may be avoidable. This second goal may seem overly ambitious to some readers, while others will judge it likely to yield only painfully obvious answers.

The research behind this article suggests that many avoidable causes of death *are* painfully obvious, but no less painful, therefore, to the people who die. Some avoidable causes are more surprising. Yet the ultimate aim of this article is not to serve up investigative coups, but to catalog the evolving causes of death in antiretroviral-rich countries at this point in the epidemic as a handy reminder for HIV clinicians and the people whom they treat.

What kills people with HIV today?

Because potent antiretrovirals can keep CD4 counts above the danger zone where opportunists operate, deaths with classic AIDS diseases such as PCP, Kaposi's sarcoma (KS), and cytomegalovirus (CMV) infection have plunged in adequately treated people. This pervasive trend fosters the notion—confirmed in some small cohorts—that non-AIDS diseases have caught up with (and sometimes surpassed) standard AIDS-defining diseases as causes of death. For example:

- A study of 255 deaths of people with HIV from 1995 through 1999 at the University Hospitals of Cleveland found an AIDS-defining cause of death in 60 percent in 1995 versus 31 percent in 1999 ($P < 0.001$).[13] For the same two years, the proportion of deaths unrelated to HIV rose from 5 percent to 19 percent.
- At Chicago's Cook County Hospital, where the HIV population is 73 percent African American, 14 percent Latino, and 33 percent female, death certificates cited non-HIV causes in 13 percent of men and 21 percent of women in 1996 compared with 31 percent of men and 33 percent of women in 1999.[14] HIV-related deaths dropped accordingly.
- At Parkland Memorial Hospital in Dallas, a comparison of deaths of 210 inpatients with HIV in 1995 and 1999-2000 charted a drop in "HIV-associated illness" as the cause from 62 to 47 percent ($P = 0.03$) and a drop in AIDS-defining illness from 51 to 38 percent ($P = 0.058$).[7] Meanwhile, the proportion of non-AIDS-related causes of death climbed from 34 to 48 percent ($P = 0.048$).

But other recent cohort studies show little slippage in proportions of people dying because of AIDS definers:

- Among 422 deaths of HIV-infected people in France during 2000, 51 percent involved at least one AIDS-defining illness, most often wasting, non-Hodgkin lymphoma (NHL), CMV, and PCP.[15]
- Analysis of 204 deaths of people attending an Atlanta clinic showed a significant drop in mortality from 1995 to 2000, but no significant change in the main causes of death—infection, organ failure, neoplasia, and end-stage AIDS.[16]

So what's happening? Are non-AIDS deaths replacing AIDS deaths or not? *IAPAC Monthly*'s unscientific sampling of HIV clinicians and clinical researchers suggests one answer. AIDS-defining causes of death remain plentiful today for three reasons, this survey indicates (Table 1):

1. Because many people—often substance abusers and people with mental illness—are unable to stick with an antiretroviral regimen, they never stop HIV's assault on the immune system and die with classic AIDS diseases.
2. A large proportion of people dying with HIV today go undiagnosed until they have advanced, unsalvageable AIDS.
3. People still die from NHL, an AIDS-defining disease.

Table 1. **Clinician survey results: Most important causes of death in people with HIV today**

	Number of times cited (n = 29)
Liver complications	25
Poor adherence	20
Failure to diagnose HIV infection until disease is advanced	20
Non-Hodgkin lymphoma*	15
Non-AIDS cancer	14
Cardiovascular complications	8
Care by clinician with limited HIV experience	7
Bacterial infection	6
Illicit drug overdose	6
Antiretroviral toxicity	6
Kidney complications	4
Wasting*	4
Antiretroviral interactions with illicit drugs	4
Antiretroviral interactions compromising antiviral efficacy	2
Tuberculosis	2
Recurrent bacterial pneumonia*	2
Septicemia	2
Suicide	2
Treatment interruptions	2

*AIDS-defining conditions.
See Acknowledgments for a list of respondents.

Along with those AIDS-defining causes, liver disease—usually kindled by hepatitis C virus (HCV) coinfection—kills a substantial proportion of people with HIV. In an interview with *IAPAC Monthly*, Daniel Kuritzkes (Brigham and Women's Hospital, Boston) explained that most people who die with AIDS despite antiretroviral access "are coming into treatment late or are unable to comply with therapy. The most challenging patients—usually active substance abusers—are in and out of care, on and off therapy, and keep coming in with recurrent *Pneumocystis*, toxo, cryptococcal meningitis, those kinds of things. They probably would do well if they could get on therapy and stay on it.

"A much smaller group in that same cause category consists of people who have highly resistant virus and are slowly progressing and dying of AIDS.

"The other big category includes the people dying because of liver disease, usually with hepatitis C."

In an e-mail note, W. Christopher Mathews (University of California, San Diego) added another contributor to the sustained death rate from AIDS definers—age. People "over 55 or so," he observed, tolerate classic opportunistic infections more poorly than younger people, especially when the diagnosis comes late.

Three large studies—two involving cohorts and one analyzing death certificates—supply some statistics that flesh out these clinical impressions. Scrutinizing deaths of 1,826 EuroSIDA cohort members in 1994-1995 ("pre-HAART"), 1996-1997 ("early HAART"), and 1998 or later ("late HAART"), researchers found that the

proportion of deaths from non-HIV causes rose from 22.6 percent in 1994 to 51.6 percent in 2000 and later ($P < 0.0001$).[4] In the same two periods, the proportion of HIV-related deaths slumped from 54.0 percent to 16.7 percent ($P < 0.0001$). But the incidence of deaths before an AIDS diagnosis in the cohort dropped from a low 3.1 per 100 person-years in 1995 to 1.1 per 100 person years in 2000-2001. The relative proportion of these non-AIDS deaths grew only because the overall incidence of death plunged from 21.6 per 100 person-years in 1995 to 2.7 in 2000-2001.

The CASCADE Collaboration of 20 European and Australian HIV cohorts gauged the effect of seroconversion year on the risk of an AIDS diagnosis or death without AIDS in 6,941 people with known seroconversion dates from 1979 through 2001.[17] To analyze these changes the CASCADE team used a "competing risks model" that allows for the fact that a rising incidence of one AIDS disease may simply reflect a falling incidence of another disease. Compared with 1994-1996, the researchers traced a significant reduction in the incidence of all major AIDS diagnoses, but not in death without AIDS or death from minor AIDS-defining illnesses (see note 18).

The CASCADE authors argue that some studies may fail to spot drops in particular AIDS diagnoses because they do not use a competing risks model or because they include too few diagnoses to identify significant changes. But the CASCADE study addresses only first AIDS diagnoses—not which AIDS diagnoses may be the proximate causes of death. For example, the authors observe, they found a significant drop in lymphoma as a first AIDS diagnosis after 1997, but that could mean lymphoma arises more often as a later AIDS diagnosis. So if people now survive an AIDS-defining disease like esophageal candidiasis but succumb to lymphoma, the cancer may kill them.

Notably, the one type of death measured in the CASCADE study—death without AIDS—did not drop during the four seroconversion periods analyzed:

- 1979-1990: 9.4 deaths without AIDS per 1,000 person-years
- 1991-1993: 10.0 deaths without AIDS per 1,000 person-years
- 1994-1996: 13.4 deaths without AIDS per 1,000 person-years
- 1997-2001: 11.4 deaths without AIDS per 1,000 person-years

In a multivariate analysis adjusting for gender, age, and HIV exposure category, the risk of death without AIDS did not vary significantly between the 1994-1996 seroconversion group and the 1997-2001 group. In other words, across these 20 European and Australian cohorts, the rate of non-AIDS causes of death stayed constant through 2001.

A different kind of study, one analyzing thousands of death certificates of HIV-infected people dying in the United States from 1987 through 1999, did find a jump in the proportion of deaths with an underlying cause unrelated to HIV.[19] But after 1995, the CDC charted sharp drops in the absolute number of deaths from: (1) HIV infection as the "underlying cause," (2) AIDS-defining disease, and (3) "other underlying causes." There were four exceptions to declines in deaths from other underlying causes:

- Hepatitis B: from 226 deaths in 1997 to 324 in 1999
- Hepatitis non-A/non-B (including C): from 476 deaths in 1997 to 807 in 1999
- Liver cancer: from 33 deaths in 1997 to 47 in 1999
- Other liver disease: from 1,330 in 1997 to 1,432 in 1999

Hepatitis outranks other death threats

The CDC's finding of surging liver-related mortality in people with HIV[19] would not surprise the 29 clinicians *IAPAC Monthly* polled on leading causes of death today. The survey included a long list of causes culled from recent literature on HIV mortality and presented in random order. Respondents were asked to check off which causes "have proved most important in your experience." Two physicians marked every cause, while most picked four or five. Twenty-five of the 29 checked off "liver complications" and usually specified HCV infection. Table 1 ranks the results.

The HIV literature is rife with reports on liver problems—often hepatitis coinfection—and mortality. Most studies saw a surge in the proportion of liver-related deaths since the dawn of potent antiretroviral therapy, though there are exceptions. A chart review of 262 University of Basel inpatients found no jump in the rate of liver failure as the cause of death from pre-HAART days (1994-1996) to the HAART era (1997-1999).[20] But a much larger Swiss HIV Cohort Study determined that HCV coinfection greatly raises the risk of death in people successfully treated for HIV.[21] This analysis involved 2,318 HCV-negative people and 1,645 with HIV plus HCV. The Swiss team found that the "excess death rate" (compared with the general population) in people without HCV and successfully treated HIV was lower than the excess death rate in successfully treated cancer patients without HIV. But the death rate among people with HCV and successfully treated HIV jumped above the rate in successfully treated cancer patients.

In the *IAPAC Monthly* survey, Swiss HIV Cohort Study investigator Bernard Hirschel (University Hospital Geneva) rated the listed causes of death from 1 (least frequent) to 5 (most frequent). He assigned a 5 only to liver complications "linked to hepatitis C and intravenous drug use." He gave a 3 to "antiretroviral interactions compromising antiviral efficacy," explaining that "patients with end-stage liver failure are especially difficult to treat." At London's Chelsea and Westminster Hospital, Graeme Moyle estimated that liver problems account for 40 percent of deaths in people with HIV—the leading cause by far.

At a few centers in the United States, HCV infection and other hepatic problems have not emerged as a leading killer. University Hospitals of Cleveland researchers found that liver failure caused the deaths of only 8.3 percent of those dying in 2001, and they saw no rise in

liver-related deaths over recent years.[22] At Parkland Memorial Hospital in Dallas, mortality from end-stage liver disease did not change from 1995 to 1999-2000.[7] And from the Owen Clinic in San Diego, Mathews wrote to *IAPAC Monthly* that, "despite all the reports of HCV-related mortality, we haven't seen as much as might be expected given a 24 percent overall coinfection rate (70 percent among our injecting drug users with HIV)."

But those are the exceptions. Bigger studies consistently show jumps in the proportion of HIV-infected people dying with hepatitis and other liver problems:

- In a EuroSIDA study of 1,826 deaths from 1994 to 2001, the rate of liver-related deaths fell from 6.85 per 1,000 person-years in 1994 to 2.73 in 1998 but then began climbing again, to 3.45 in 2000 and later.[4] Since January 2000, hepatitis emerged as the leading killer in EuroSIDA, accounting for 17 percent of those who died.
- A survey of US death certificates of people dying with HIV from 1987 through 1999 saw decided gains in the proportions dying with hepatitis B or hepatitis non-A/non-B (including C) starting in 1996.[19]
- A Women's Interagency HIV Study (WIHS) involving 2,059 infected women monitored from 1994 to 2000 rated "hepatic disease" the leading non-AIDS cause of death, in 21 percent of women who died.[23]
- A six-city CDC survey of 7,188 deaths of people with HIV found a 70 percent jump in the risk of death from liver disease when comparing the pre-HAART era (1992-1995) with the HAART era (1996-2000).[24]

Studies relying on death certificates to establish the cause of death may underestimate the rate of liver-related deaths, according to Barbara McGovern and colleagues at Boston's New England Medical Center.[25] When working on their small study of increasing mortality from end-stage liver disease,[26] they were "surprised to find death certificates that reported 'acquired immunodeficiency syndrome' as the immediate cause of death when chart review clearly showed that the patient died of complications of end-stage liver disease."[25]

Can liver deaths be prevented?

Certain deaths from hepatitis and its complications can surely be prevented or at least delayed—sometimes rather simply, but often only with great effort. Among people coinfected with HCV, hepatitis therapy is suboptimal for many. "Most of them have genotype 1a," Kuritzkes explained, "so they are not responding well to interferon and ribavirin therapy." In a 106-person Spanish trial of interferon plus ribavirin for HCV infection in people with HIV, study participants with genotype 2 or 3 had HCV response rates seven times higher than people with genotype 1 or 4.[27]

Still, everyone with HIV infection should be tested for HCV, the US Public Health Service recommends,[28] because knowing a person's HCV status is critical to treating HIV infection. The guidelines also recommend vaccinating HCV-coinfected people against hepatitis A virus (HAV) and hepatitis B virus (HBV) (see note 29). These experts call for the HBV vaccine in all children with HIV (see Table 10 in reference 28). Many clinicians believe sexually active or drug-using people with HIV—even those without HCV—should get the HAV and HBV vaccines to protect them from these bloodborne viruses.

Joel Gallant (Johns Hopkins University, Baltimore) told the story of "two recent patients—both gay men—whose doctors never vaccinated them against HBV, despite the clear indications. They became infected both with HIV and HBV, developed chronic hepatitis, and ultimately died, one of cirrhosis and the other of hepatocellular carcinoma—tragically preventable deaths. I should add that both were doing very well from the standpoint of their HIV infection when they died."

As these two cases illustrate, people carrying both HIV and a hepatitis virus often respond well to antiretroviral therapy. In one US series of 162 people with HIV and HBV or HCV, 88 percent tolerated their antiretrovirals well with little evidence of toxicity on liver function tests.[30] And potent antiretroviral therapy appears to lower the risk of liver-related death far more than it raises the risk of deadly liver toxicity. A study of 285 HIV/HCV-coinfected people at the University of Bonn figured the following liver-related death rates in three antiretroviral treatment groups:[31]

- HAART: 0.45 deaths per 100 person-years
- Nucleosides only: 0.69 deaths per 100 person-years
- No antiretrovirals: 1.70 deaths per 100 person years

Five people (9 percent) taking only nucleosides and 13 taking HAART (14 percent) had severe drug-related liver toxicity, but no one died as a result. The survival benefit with HAART, the authors conclude, "seems to outweigh by far the associated risks of severe hepatotoxicity."[31]

Results like these inspired several *IAPAC Monthly* survey respondents to urge an assertive approach to both diagnosis and treatment of HCV infection in people with HIV. "We need to be more aggressive with treatment of HIV-HCV," wrote José Arribas (Hospital La Paz, Madrid). "Even if the efficacy is less than in HCV-monoinfected people, treatment might be cost-effective."

Yet the risks are there. Nevirapine's (NVP) label carries a "black box" warning about fatal hepatotoxicity. Efavirenz (EFV), stavudine (d4T),[32] and the protease inhibitors (PIs)—especially ritonavir (RTV)-boosted PIs[30]—can also rile liver enzymes. Tight monitoring of liver function makes sense for people taking these drugs, although even "close out-patient supervision and monitoring of liver function" did not prevent acute liver failure (and five deaths) attributed to antiretroviral toxicity at King's College Hospital in London.[33] Still, deaths due to viral hepatitis far outnumber those due to antiretroviral toxicity.

As in the two cases cited by Gallant, uncontrolled hepatitis can lead to cirrhosis and liver cancer. At Stanford University's HIV clinic, Nancy Shulman spotted two cases of hepatocellular carcinoma in people referred to her with well-controlled HIV infection, but with cirrhosis and hepatitis virus coinfection. Both died.

With earlier diagnosis and successful treatment of HCV infection, she e-mailed *IAPAC Monthly*, both cases "might have been transplantable or operable."

The past year has brought good news on the feasibility—and success—of liver transplants in people with HIV infection. One comparison of 24 HIV-infected transplant recipients with age- and race-comparable HIV-uninfected recipients found equivalent survival after 12, 24, and 36 months.[34]

Alcoholism complicates the management of anyone with HIV infection. And for people who also carry a hepatitis virus, drinking compounds threats to the liver. Hepatitis expert Maurizio Bonacini (California Pacific Medical Center, San Francisco) tells people beginning HCV therapy that the first step is to quit drinking.[35] If they can't make that commitment, he believes, they're unlikely to follow other advice.

Because of the shortcomings of anti-HCV therapy, Renslow Sherer (University of Chicago Hospitals) stressed in an e-mail note to *IAPAC Monthly*, "it is important for patients and doctors to understand that a physician can significantly reduce the risk of chronic liver disease and mortality by persuading and helping the patient to stop all alcohol intake."

No one has the final word on when to treat HCV infection in people with HIV, and the best treatment available today—pegylated interferon plus ribavirin—fails all too often. Partly as a result, said some respondents to the survey for this article, HCV-coinfected people often go untreated. But last year two groups—an ad hoc international panel[36] and the British HIV Association[37] (BHIVA) proposed thoughtful guidelines for managing HCV in people with HIV. BHIVA also outlined management advice for HIV/HBV-coinfected people.[38]

Briefly, the international panel makes these points:

1. Screen for HCV antibodies in everyone with HIV infection.
2. People with genotypes 1 and 4 and no or minimal fibrosis may wish to delay therapy until more effective anti-HCV drugs are available.
3. The best candidates for HCV therapy are those with persistently elevated alanine aminotransferase (ALT), a CD4 cell count above 350 cells/mm^3, and a viral load below 50,000 copies/ml.
4. People with persistently normal ALT should receive therapy for HCV only if they have fibrosis, or in a clinical trial if they do not have fibrosis.
5. People with a CD4 count below 200 cells/mm^3 are generally poor candidates for HCV therapy.
6. People with compensated cirrhosis are candidates for HCV therapy, but those with hepatic decompensation should be considered for liver transplantation.
7. Consider liver transplantation in all people with HCV-related end-stage liver disease and without advanced HIV disease.
8. Substance abuse and severe neuropsychiatric conditions must be addressed before beginning HCV therapy.

Some clinicians try to avert the depressive effects of interferon by coadministering a selective serotonin reuptake inhibitor (SSRI). Johns Hopkins hepatitis expert Stuart Ray starts an SSRI along with interferon in people with a history of alcoholism or a personal or family history of depression.[35] In others he starts an SSRI only if a person becomes depressed while taking interferon.

BHIVA suggests treating for HCV coinfection before starting antiretrovirals, when possible, in people with a CD4 count above 200 cells/mm^3 because pretreating HCV lowers the risk of liver toxicity when antiretrovirals start.[37] For people who have already started antiretrovirals when HCV is diagnosed, BHIVA recommends delaying HCV therapy until the CD4 count climbs over 200 cells/mm^3. The British experts advise clinicians that didanosine (ddI) with or without tenofovir (TDF) should be used "with extreme caution" in people taking ribavirin for HCV.

Finally, Johns Hopkins' Gallant reminded *IAPAC Monthly*, the public health system already has a tool that can prevent infection with hepatitis viruses—and with HIV as well: needle exchange. Overcoming conservative bias against needle exchange programs in countries such as the United States will take years of concerted effort. But that is no reason not to begin.

Steps to prevent liver disease deaths:

- *Test HIV-infected people for HAV, HBV, and HCV.*
- *Vaccinate people for HAV and HBV if they are not already infected or exposed (see note 29).*
- *Consider treatment for HCV infection. (Consult guidelines offered by an international panel[36] and the British HIV Association.[37])*
- *Finds ways to help people with hepatitis stop drinking alcohol.*
- *Begin monitoring liver enzymes when starting antiretrovirals.*
- *Consider liver transplants for people with advanced liver disease.*

Bad adherence can kill

Before people with HIV began taking potent antiretrovirals, the retrovirus killed nearly everyone it infected. In countries that cannot provide antiretrovirals for HIV-infected people, those people are dying today. So it should be no surprise that people who can get antiretrovirals—but take them haphazardly or not at all—will die as well.

Anyone who doubts that bad adherence kills might consult two studies in British Columbia, where antiretrovirals are free. The first involved 1,281 antiretroviral-naive adults beginning triple therapy between August 1996 and December 1999.[9] Defining "intermittent therapy" as filling fewer than 75 percent of prescriptions in the first year of treatment, University of British Columbia researchers used a multivariate model to isolate only two factors that raised the risk of death: Each 100-cell decrement

in pretreatment CD4 count raised the risk 1.31 times, and intermittent therapy raised the risk 2.90 times ($P < 0.001$ for both). The researchers ran a subanalysis on people with at least one year of follow-up to eliminate a statistical bias called downward drift—the chance that less frequent use of antiretrovirals in the first year simply marked more rapid HIV disease progression. This subanalysis confirmed the tie between poor adherence and death.

A more recent and larger study by the same group found that poor adherence outweighed baseline CD4 count in predicting mortality.[39] Everyone in the 1,422-person cohort started potent antiretroviral therapy between August 1, 1996 and July 31, 2000. Follow-up continued until March 31, 2002. Again the Vancouver team figured adherence by prescription filling and limited statistical scrutiny to the first year of treatment.

A Kaplan-Meier analysis showed that starting antiretrovirals with 200 or more CD4 cells/mm^3 did not prolong survival in the 485 people who had at least 95 percent adherence. But at the 75 percent adherence level, starting treatment even with 350 cells/mm^3 or more did not prolong survival in poor adherers. Adjusted relative hazards of death for people with less than 75 percent adherence measured 2.80, 3.05, and 3.21 for people beginning antiretrovirals with 350 cells/mm^3 or more, 200 to 349 cells/mm^3, and fewer than 200 cells/mm^3. The researchers got the same results when they eliminated accidental deaths from the analysis and used the 95 percent adherence cutoff. They believe their findings suggest that bad adherence, rather than how far the baseline CD4 count exceeds 200 cells/mm^3, "may be the strongest determinant of patient survival."

Reasons for poor adherence in places with ready access to antiretrovirals could fill a book—and should. But substance abuse of one kind or another proved the most-cited in the *IAPAC Monthly* survey. In Miami, Dushyantha Jayaweera (University of Miami) cited crack cocaine as the leading problem; in St. Louis, Judith Aberg (Washington University) named cocaine and alcohol; in San Diego, Mathews sees crystal methamphetamine as "the single biggest barrier to effective HIV care in our clinic," particularly among gay and bisexual men. At Baltimore's Johns Hopkins Hospital, Gallant has an HIV ward "full of people who often die because of their inability to take medications" for a host of reasons—drug abuse, mental illness, and inadequate housing, to name three.

All HIV clinicians treating poor people in rich countries recognize these often incorrigible problems. From Cincinnati, Carl Fichtenbaum (University of Cincinnati) wrote of the dire need for "comprehensive life-changing programs to alter adherence problems" and "adequate health insurance to allow access to care on an ongoing basis." But sometimes even the best services don't suffice. From the Veterans Administration Medical Center in San Diego, Douglas Richman noted that only six people being treated for HIV died last year—about 1 percent of the population. They all had "significant emotional and/or substance abuse problems," which prevented them from adhering to antiretroviral regimens despite abundant counseling resources at the facility.

On the other hand, many HIV clinics would consider 1 percent annual mortality a worthy accomplishment. The extra counseling and support that a veterans hospital can offer probably do make regular pill takers out of many people with disorganized lives—people who might otherwise die. And certainly there are ways to teach adherence to substance abusers. At the IAPAC Sessions 2003, Patricia Kloser (New Jersey Medical School, Newark) explained that "you have to teach that person to be a patient."[40] She may try to teach adherence by first prescribing a vitamin or, if indicated, PCP prophylaxis, and monitoring the patient closely. Others use initial appointment keeping as a gauge of likely adherence.

Pilot studies of directly observed therapy (DOT) and modified DOT with antiretrovirals show that it can improve adherence and yield virologic benefits in hard-to-treat populations including prisoners,[41] former prisoners,[42] injecting drug users,[43,44] and people in methadone maintenance programs.[45] Antiretroviral DOT has become more feasible with today's once-daily regimens, such as amprenavir (APV)/RTV plus ddI/lamivudine (3TC)[44] and efavirenz (EFV) with 3TC and abacavir (ABC).[45]

The most common once-daily regimens, Gallant suggested, are:

1. ABC or TDF or ddI, plus
2. 3TC or emtricitabine (FTC), plus
3. EFV or atazanavir (ATV) or ATV/RTV

Such regimens will ease adherence for anyone taking antiretrovirals.

DOT is expensive in developed countries. It requires a dedicated crew of social workers. And how well people continue taking antiretrovirals after DOT stops will only be learned from ongoing studies. But if modified DOT can work in the grinding poverty of rural Haiti,[46] it should not be written off too readily in poor inner cites and rural regions of wealthy lands.

One can safely bet that all clinicians reading this article became convinced long ago that adherence matters mightily in controlling HIV. Indeed, research shows that clinicians with more HIV experience do better in promoting antiretroviral adherence.[47] That is only one reason why all should encourage efforts to establish a certificate of qualification that will identify physicians with expertise in HIV infection. But even 20-year veterans of the HIV wars can probably bear to scan the following list of adherence tips, mustered from recent publications and *IAPAC Monthly* survey responses.

Fateful impact of a late diagnosis

In the *IAPAC Monthly* survey, late diagnosis of HIV infection tied for second as the most frequently cited cause of death in developed countries today (Table 1). At the Stanford University clinic, Andrew Zolopa sees more than a few people with acute opportunistic infections "who have either been tested and fell through the cracks of the healthcare system or were never tested." From San Diego, Mathews wrote that "we have quite a few undocumented people coming across from Mexico in

Some reminders on promoting adherence:

- *Establish an adherence education policy that involves all appropriate professionals in the clinic and pharmacy.*
- *Find out what adherence education sessions are offered by local institutions and community groups, determine which are the most useful, and use them.*
- *Copy, consider, and distribute the helpful adherence advice from the latest US Department of Health and Human Services antiretroviral guidelines.*[48]
- *Get to know each treatment candidate and assess his or her adherence potential before starting antiretrovirals.*
- *Address potential obstacles to adherence (such as substance abuse, depression, and inadequate housing) before starting therapy.*
- *Don't start therapy until you're convinced that a person is ready and "buys in" to the idea of treatment.*
- *Make sure a person starting antiretrovirals understands the long-term consequences of poor adherence and the probability that the first regimen offers the best chance of success.*
- *Explain potential side effects of drugs in a regimen and take appropriate steps to prevent them or address them promptly if they arise.*
- *Emphasize that starting antiretroviral therapy sometimes requires a "trial-and-error approach" and that you'll manage side effects or switch away from poorly tolerated drugs until the regimen is satisfactory.*
- *Expect people to misunderstand treatment instructions. Ask them to repeat the instructions in their own words and give them written drug information and dosing instructions.*
- *Recruit family and friends to support adherence.*
- *Monitor adherence at every clinic encounter.*
- *Watch for pill fatigue and waning adherence even in the most motivated people.*
- *Consider the impact of new diagnoses—such as depression, liver disease, and recurring substance abuse—on adherence.*

advanced disease stages who are too sick to survive the initial infections but could have been salvaged if they came in earlier."

Often these "late presenters" come from the same groups that have severe adherence problems, noted Phillip Keiser (Parkland Memorial Hospital, Dallas)—substance abusers and people with untreated mental illness. These are people "who do not seek regular care," Keiser finds, and "are only seen in the ER when they are sick." Mortal delays in seeking care for HIV seems common throughout the developed world, from Mike Youle's Royal Free Hospital in London, to Jonathan Schapiro's Sheba Medical Center in Tel Aviv, to Pedro Cahn's Fundación Huesped in Buenos Aires. In France, Aquitaine cohort researchers found that 15 percent of cohort members who died in 1998 and 1999 had never taken an antiretroviral.[49] US researchers attributed excessive HIV-related mortality in Florida prisons to late diagnoses of infection.[50]

Poor public education and little knowledge about HIV explain why some people don't seek care until an advanced opportunistic disease strikes. But a distinct set of HIV-infected people "are aware of their HIV status," wrote Aberg from St. Louis, "but for numerous reasons don't access care and then present with advanced disease." Some of them, she added, still refuse antiretrovirals and even OI prophylaxis, "despite all our educational interventions."

Others avoid the clinic because of poor health coverage—or embarrassment. Zolopa reported the case of a man who "did not seek out care because of insurance issues" and "ended up with severe cryptococcal disease." He started antiretrovirals and responded well, with undetectable viremia by three months. But he "continued to suffer from complications of his cryptococcal meningitis, leading to blindness and death." In Düsseldorf, Stefan Mauss (Center for HIV and Hepatogastroenterology) saw a man with "late-stage anorectal cancer who was shy to present his giant anal condylomata."

The individual clinician can do little for people who doggedly avoid the clinic or disavow care. But sometimes HIV physicians may interact regularly with such diehards and miss the opportunity to encourage testing or treatment. From Chicago, Sherer relayed the case of a man who worked as an HIV care manager in another city. He knew his HIV status for five years but avoided treatment despite *daily* counseling others on the benefits of therapy. Eventually he returned to Chicago "with seizures and rapidly deteriorated and died with progressive multifocal leukoencephalopathy in eight weeks." Why? "Denial," Sherer suggested, "is a powerful motivator."

From Geneva, Hirschel added that many who deny the gravity of their HIV infection "are influenced by an unrealistically gloomy view of the side effects and complexity of HAART." That sentiment, he proposed, "is fueled by the politically correct line, which is to emphasize side effects and complexities of treatment, so as to keep HIV alive as a serious threat in the minds of the public, and to scare them away from ditching condoms."

People who tenaciously refuse care cannot be helped unless their tenacity can be sapped. Just keeping these people coming back for visits (as Aberg discovered in a case described below) can sometimes pay off. And plenty of people who go undiagnosed because they never suspect they have HIV can surely be stopped well short of death's door. Zolopa believes "programs that integrate testing with care and target high-risk disenfranchised groups could have a very positive impact." Sherer hopes that the new rapid HIV tests "will help both identify infected people and get them immediately into care."

Those are certainly among the goals in the CDC's campaign to expand diagnoses of HIV with a four-part strategy:[51]

- Incorporating HIV testing into routine medical care
- Diagnosing HIV infection in nonmedical settings
- Contacting partners of people infected with HIV
- Making HIV testing a regular part of prenatal care and testing all newborns whose mother's HIV status is unknown

A few ways to promote earlier HIV diagnosis and treatment:

- *Make voluntary counseling and testing a routine part of medical practice.*
- *Urge HIV-infected people to encourage their sex partners—and drug-sharing partners—to seek medical care.*
- *Maintain a high index of suspicion for diagnosis of HIV and AIDS diseases in people with inadequate or no health coverage.*
- *Review the CDC's 2003 recommendations on HIV diagnosis and consider which parts fit into your practice.*[51]
- *Seek out peer support groups for infected people who refuse treatment.*
- *Schedule follow-up monitoring visits for infected people who refuse treatment, and keep the pressure up.*

Announcing the program, CDC chief Julie Gerberding called it "simply unacceptable that 40,000 people in this country become infected with HIV each year, and it's intolerable that about one fourth of those infected with HIV don't know they're infected and therefore are not receiving appropriate medical care."

The CDC figures that one third of those who got a positive HIV test result in 2000 didn't return for treatment.[51] But more than 90 percent with a positive reading on a rapid HIV test came in for a confirmatory assay.[52]

AIDS cancers and non-AIDS cancers

Most large cohort studies detect a drop in new diagnoses of NHL, and a drop in NHL deaths, since more potent antiretrovirals began bolstering immune systems. But as the proportion of deaths from classic AIDS diagnoses like PCP and toxoplasmosis fell, often-obstinate NHL climbed through the rankings to emerge as a leading killer. Fifteen of 29 physicians responding to the *IAPAC Monthly* survey rated NHL a leading cause of death in their clinics (Table 1). Non-AIDS cancers ranked just behind NHL in the survey, with 14 clinicians branding these neoplasms as a fatality leader.

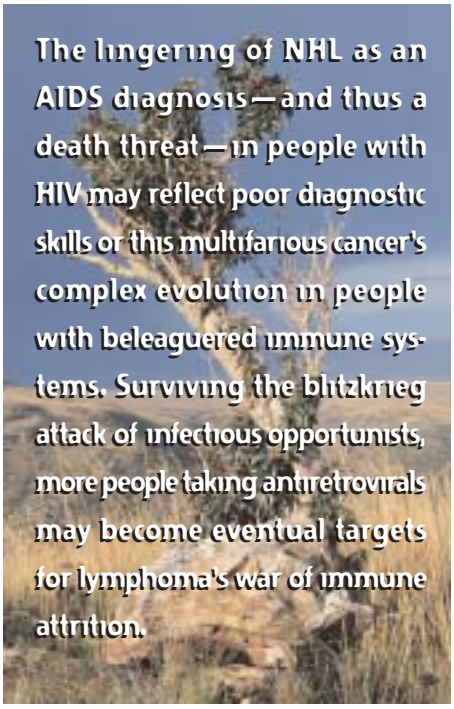
A review of the literature on NHL in people with HIV (Table 2) traces several trends since people started taking HAART:

- Sharp drop in incidence (new diagnoses) of NHL after HAART arrived[17,54,56,59,63]
- Better response rate to chemotherapy in people responding to HAART[55,58,64]
- More aggressive anticancer therapy feasible in people taking HAART[57,64,65,67]
- Longer survival with NHL in people taking HAART[55,56,58,60,62,65,68]
- Lower NHL incidence and longer survival with HAART linked to higher CD4 counts, lower viral loads, or both[60,61]

During 26,764 person-years of follow-up in the EuroSIDA cohort, the incidence of NHL plunged from 1.99 cases per 100 person-years before September 1995 to 0.30 cases per 100 person-years after March 1999.[59] HAART appeared to explain the drop. NHL incidence sank from 0.88 cases per 100 person-years during cohort members' first 12 months of HAART to 0.45 cases after more than 24 months ($P = 0.004$). An adjusted Cox model for everyone taking HAART tied the drop in NHL diagnoses to higher CD4 counts and lower viral loads.

In the CASCADE Collaboration study involving 6,941 people with known seroconversion dates from 1979 through 2001, NHL as a first AIDS diagnosis (in 98) dropped by 48 percent among people who picked up HIV in 1997-2001 compared with those infected in 1994-1996 ($P < 0.05$).[17] An analysis of US death certificates found that the *proportion* of deaths due to NHL rose from 1987 through 1997, surpassing even KS at that point.[19] But the NHL death rate began dwindling after that.

Meanwhile, a raft of studies showed that people with NHL began living longer after they started HAART,[55,56,58,59,62,64,68] apparently because HAART favored a better response to chemotherapy,[55,58] enabled people to try more aggressive cancer therapies,[57,64,65,67] and favored survival by promoting immune recovery.[59,60]



But these findings do not hold true in every cohort. Studies of 5,017 Australians with AIDS[61] and of 7,188 HIV-related deaths in the United States[24] charted jumps in the *proportion* of people with NHL as a first diagnosis[61] and in the *proportion* of NHL deaths[24] when comparing HAART years with pre-HAART days (Table 2). Both of these findings may reflect *disproportionate* drops in first diagnoses of infectious AIDS opportunists and in deaths from opportunistic infections. Even so, such findings probably account for the valid perception that NHL has gained rank as an AIDS-defining disease and as a cause of death since the arrival of HAART. Those are good reasons,

Table 2. **Effect of HAART on NHL incidence, response to chemotherapy, and mortality**

*First author**	*Site(s)*	*Type of study*	*n*	*Years*	*Main findings*
Ledergerber[53] (7/1999)	Switzerland	Retrospective observational	6,638 (total cohort members studied)	1992-1994 vs 7/1997-6/1998	Little change in progression to NHL in early HAART years, but sharp drop in progression to KS.
ICHC[54] (11/2000)	North America, Europe, Australia	Retrospective observational	47,936 (total cohort members studied)	1992-1996 vs 1997-1999	Incidence of NHL drops 42% in HAART era.
Navarro[55] (3/2001)	Barcelona	Retrospective observational	41 without HAART, 17 on HAART	1988-1996 vs 1996 and later	Higher response rate to CHOP and longer event-free and overall survival in people on HAART.
Chow[56] (4/2001)	Frankfurt	Retrospective observational	257	1983-1999	NHL incidence drops and survival increases in HAART era.
Ratner[57] (4/2001)	17 US centers	Prospective observational	65	—	In people taking HAART, higher response rate and no more side effects with full-dose CHOP plus G-CSF than with reduced-dose CHOP.
Antinori[58] (8/2001)	Two Italian centers	Prospective observational	44	6/1999-12/1999	Better response to chemotherapy and longer survival in people responding to HAART.
Kirk[59] (12/2001)	Europe (EuroSIDA)	Prospective observational	8,471	1994-2000	NHL incidence drops from 1.99 cases per 100 p-y before 9/1995 to 0.30 cases per 100 p-y after 3/1999; decrease tied to higher CD4 counts, lower viral load in HAART era.
Baiocchi[60] (2002)	São Paulo, Brazil	Retrospective observational	13 without HAART, 7 on HAART	1991-2001	Longer median survival in HAART patients versus non-HAART patients correlates with higher CD4 count.
Wolfe[24] (2/2002)	Six US cities	Retrospective observational	7,188 (total deaths)	1992-1995 vs 1996-2000	*Proportion* of deaths from NHL rises 50% in HAART era.
Cascade Collaborators[17] (3/2002)	Europe, Australia	Retrospective observational	98	1994-1996 vs 1997-2001	NHL as first AIDS diagnosis drops in HAART era.
Dore[61] (4/2002)	Australia	Retrospective observational	5,017 (total AIDS diagnoses)	1993-1995 vs 1996-2000	*Proportion* of NHLs as first AIDS diagnosis rises in HAART era; no significant change in median survival in NHL group from pre-HAART to HAART.
Selik[19] (4/2002)	United States	Retrospective review of death certificates	NR†	1987-1999	NHL accounts for an increasing proportion of deaths through 1997; proportion of NHL deaths drops sharply in 1998 and 1999.
Tam[62] (4/2002)	United States (MACS)	Retrospective observational	100	1990-1999	HAART prolongs survival with NHL whether started before or after NHL diagnosis.
Eltom[63] (8/2002)	United States	Retrospective observational	—	1973-1998	Incidence of NHL types most associated with AIDS drops most steeply, while incidence of NHL types not associated with AIDS either stable or increasing.
Gerard[64] (8/2002)	Paris	Chart review	246	1/1992-12/2000	Two-year survival with NHL rose in HAART era; more intensive chemotherapy correlated with longer survival.
Molina[65] (8/2002)	Duarte, California	Case report	2	NR	Autologous stem-cell transplant feasible and effective in 2 people with HIV NHL.
Matthews[66] (10/2002)	London	Chart review	150 with AIDS-related lymphoma	1988-1995 vs 1996-1999	Incidence of and survival with AIDS lymphoma do not change in HAART era.
Re[67] (12/2003)	Italy	Prospective observational	16	NR	High-dose chemotherapy and autologous stem-cell transplant are feasible and effective in HAART responders with lymphoma.
Vaccher[68] (12/2003)	Italy	Retrospective observational	235	1988-1999	Long-term HAART versus no HAART associated with longer overall, progression-free, and disease-free survival.
Spina[69] (1/2004)	Italy	Retrospective observational	100 with HIV, 82 without HIV	1/1997- 4/2002	Overall survival with NHL shorter in people on HAART than in NHL patients without HIV; survival comparable in people who achieve complete remission.

*Month of publication or meeting report in parentheses.

†Numbers of deaths from NHL not reported. Total HIV deaths per year range from 47,977 in 1995 to 16,016 in 1999.

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; G-CSF = granulocyte colony-stimulating factor; ICHC = International Collaboration on HIV and Cancer; KS = Kaposi's sarcoma; MACS = Multicenter AIDS Cohort Study; NHL = non-Hodgkin lymphoma; NR = not reported; p-y = person-years.

Schapiro e-mailed from Tel Aviv, to maintain a "high suspicion for NHL" with "good routine physical exam and labs."

The lingering of NHL as an AIDS diagnosis—and thus a death threat—in people with HIV may reflect poor diagnostic skills or this multifarious cancer's complex evolution in people with beleaguered immune systems. Surviving the blitzkrieg attack of infectious opportunists, more people taking antiretrovirals may become eventual targets for lymphoma's war of immune attrition.

A study at London's Chelsea and Westminster Hospital involving 150 HIV-infected people diagnosed with lymphoma since 1986 spotted no drop in lymphoma incidence when comparing pre-HAART years (1988-1995) with the early HAART era (1996-1999).[66] Probably because new diagnoses of classic opportunists waned after HAART arrived, lymphoma accounted for a significantly bigger percentage of first AIDS diagnoses in the later years ($P \leq 0.0001$). These researchers found no difference in survival with lymphoma when comparing the two treatment eras, but they did link a lower nadir CD4 count and no prior HAART with development of lymphoma. These NHL predictors, they write, "may translate into a future fall in new cases," as in other cohorts.[17,54,56,59,63]

Two important points emerge from studies correlating antiretroviral therapy or anticancer therapy with NHL diagnosis and survival. First, people responding poorly to HAART run a higher risk of NHL and of a quicker death if they do get NHL. At Saint-Louis Hospital in Paris, for example, three quarters of 112 NHL diagnoses in the HAART era happened in people with poorly controlled viremia.[64] An Italian study of 44 consecutive patients treated simultaneously with HAART and chemotherapy charted complete NHL response rates in 71 percent of HAART responders and 30 percent of nonresponders.[58] Virologic response to HAART was the only variable these researchers linked to tumor response in a multivariate analysis. Studies like these suggest that people who do poorly with NHL share a trait with people who succumb to other AIDS diseases today: For one reason or another, they cannot or will not stick to their antiretroviral regimen.

Second, HAART may prolong survival with NHL because it promotes a good immune response that makes more aggressive chemotherapy possible. A US study tracked responses in 65 people previously untreated for NHL, giving 40 of them reduced-dose CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and 25 of them full-dose CHOP plus granulocyte colony-stimulating factor.[57] All patients also took d4T, 3TC, and indinavir (IDV). Complete response rates measured 30 percent in the reduced-dose group and 48 percent in the full-dose group, while side effect rates proved similar in the two groups.

The 112-person study in Paris linked improved survival with more intensive chemotherapy.[64] And the 44-person Italian study tied higher relative dose intensity of anti-NHL drugs to a reduced risk of death.[57] Small studies in the United States and Italy found that high-dose chemotherapy and autologous stem cell transplantation are feasible and effective in HIV-infected people with NHL.[65,67] The Italian researchers propose that "HIV infection should no longer preclude the opportunity of [high-dose therapy] in patients with lymphoma."

The "non-AIDS cancers" may not fit the CDC's definition of opportunistic neoplasms. But for some people with HIV infection today, they pose as grave a threat as KS did in the 1980s. Invasive cervical cancer became such a big threat in women with HIV that the CDC added it to the "AIDS-defining" list. Some think that anorectal cancer deserves the same upgrade.[70]

From Geneva, Hirschel wrote that Hodgkin lymphoma "should be counted among the AIDS-linked cancers" and noted that lung cancer has become more frequent as people with HIV age—and often continue to smoke. In Madrid, Arribas listed Hodgkin lymphoma, lung cancer, and anorectal cancer—along with cervical cancer—as growing threats. Late-stage anorectal cancer killed one of Mauss's patients in Düsseldorf because he was too embarrassed to seek care for large anal condylomata.

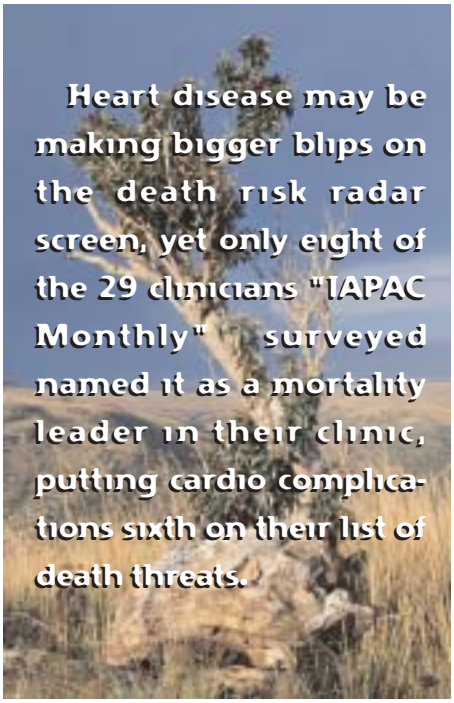
Cohort studies and other surveys that count deaths from non-AIDS cancers suggest that 10 to 20 percent of deaths in the HAART years may be traced to these malignancies, depending on how deaths are counted. Analysis of 107 deaths in the French Aquitaine cohort in 1998 and 1999 attributed 12 of them (11 percent) to non-AIDS cancers.[8] Non-AIDS malignancies accounted for 13 percent of non-AIDS-defining causes of death from 1994 through 2000 in the US

Tactics to trim the odds against NHL and non-AIDS cancers:

- *Maintain a high suspicion for non-Hodgkin lymphoma (NHL) in people with HIV during physical exams and laboratory work-ups.*
- *With your consulting oncologist, consider more aggressive therapies for NHL in HAART responders.*
- *Remember that some non-AIDS-defining cancers pose a threat to people with compromised immunity.*
- *Follow current cervical cancer screening guidelines.[73]*
- *Screen for cervical intraepithelial neoplasia, a precursor to invasive cervical cancer, in women.[74]*
- *Screen for anal intraepithelial neoplasia—a precursor to anal cancer—in all men who have sex with men, regardless of HIV status.[75]*
- *Consider screening for anal intraepithelial neoplasia in the following groups:[75]*
  - *Women with cervical cancer, high-grade vulvar disease, or cancer*
  - *All HIV-infected men and women, regardless of sexual orientation*
  - *People with perianal condyloma acuminata*
  - *Transplant recipients*
- *Stress the risk of lung cancer in people with HIV as a key reason to stop smoking.*

Women's Interagency HIV Study (WIHS) cohort.[23] Analysis of 863 deaths in France among HAART responders with a CD4 count above 200 cells/mm3 and a viral load under 500 copies/mL blamed non-AIDS cancers (usually lung or anorectal cancer) for 19 percent.[71]

The proportion of deaths due to non-AIDS cancers grew significantly in a San Francisco survey of 5,234 HIV-related deaths from 1994 (6.4 percent) through 1998 (10.9 percent, $P < 0.01$).[72] The main non-AIDS cancers were lung cancer, Hodgkin disease, liver cancer, and anal cancer. The US death certificate analysis of people with HIV found a stable proportion of deaths from cancers of the lung, bronchus, and trachea through 1995, an increase in 1996 that peaked in 1998, and a fall in 1999.[19] Because some of these studies count hepatocellular carcinoma among non-AIDS cancers, they include deaths that can be traced back to hepatitis virus coinfection.



How big is the threat from heart disease?

The risk of cardiovascular disease in people with HIV infection grabbed the attention of many protease inhibitor prescribers and takers when it became clear that most PIs—especially with a lift from RTV—can send lipids skyward. (Atazanavir is an exception.) Big cohort studies linking a growing risk of myocardial infarction with more years taking PIs[76] or combination antiretroviral therapy (with or without PIs)[77] stoked those concerns.

But heart disease is no new affliction in people with HIV infection. By 1999 heart disease had become the fifth leading cause of death among people with HIV, according to a US death certificate survey (trailing "unspecified pneumonia," septicemia, liver disease, and kidney disease).[19] Among non-AIDS deaths from 1994 through 2000 in the US Women's Interagency HIV Study, cardiac disease tied for fourth place (along with accident, suicide, or homicide) by accounting for 11 percent of deaths.[23] In the 2000 French HIV mortality study, cardiovascular disease led to 16 percent of deaths in people responding well to HAART.[71]

And the rate of heart-related deaths among people with HIV is on the rise. A survey of six US cities found a (nonsignificant) 1.9 times higher risk of death from ischemic heart disease in 1996-2000 than in 1992-1995.[24] A San Francisco study figured that the proportion of deaths from coronary artery disease in people with HIV rose from 0.8 percent in 1994 and 0.5 percent in 1995 to 1.2 percent in 1996, 1.3 percent in 1997, and 1.8 percent in 1998 ($P < 0.01$).[72] A EuroSIDA study stretching from 1994 to 2000-2001 ranked myocardial infarction as the second leading non-AIDS, nonsuicide cause of death (after hepatitis) since January 2000.[4]

A study looking at serious or life-threatening complications among 2,947 people enrolled in five clinical trials from 1996 through 2001 rated cardiovascular complications just behind liver problems and neutropenia/anemia.[6] But the risk of death from heart disease was higher than with any other complication (hazard ratio 7.08, $P = 0.0001$), just higher than the death risk from AIDS (hazard ratio 6.95, $P = 0.00001$).

Heart disease may be making bigger blips on the death risk radar screen, yet only eight of the 29 clinicians *IAPAC Monthly* surveyed named it as a mortality leader in their clinic, putting cardio complications sixth on their list of death threats (Table 1). That level of concern reflects the low incidence of myocardial infarction in the multicohort DAD study (3.5 per 1,000 person-years)[77] and the French hospital study (1.6 per 1,000 person-years for men taking PIs for 18 to 29 months, and 3.4 per 1,000 person-years for those taking PIs longer, compared with an expected rate of 1.1 per 1,000 person-years in the French male population).[76] Of the 126 infarctions counted in DAD, only 36 (29 percent) proved fatal, and only 6 percent of deaths in the cohort resulted from infarction. The French team did not report how many of the 60 heart attacks in their analysis were fatal.

Clinicians at Boston's Brigham and Women's Hospital have seen only a few cardiovascular deaths in people with HIV, Kuritzkes told *IAPAC Monthly*. "They've generally been in people who have other underlying risk factors—diabetes, hypertension, and kidney disease," Kuritzkes says. "And it's generally in people who are of an age where you would expect to begin seeing cardiovascular mortality, which makes it very hard to sort out if it's an increased risk due to antiretroviral therapy or HIV infection."

A recent survey of a US managed care database backs Kuritzkes' clinical impression. Analyzing 174 hospital admissions of 18- to 90-year-olds with HIV between January 1 and June 30, 2000, the University of Cincinnati's Fichtenbaum found that 42.5 percent admitted for heart problems had hypertension and 22.5 percent had diabetes.[78] Four of five people with heart disease were men, and their age at admission averaged 55.6 years.

Although research ties both hypertension and diabetes to PI therapy, a third big contributor to heart disease has nothing to do with antiretrovirals—smoking. Among 535 people with HIV who died in France from January to June 2000, 51 percent smoked.[14] Cardiovascular disease came in third among non-AIDS causes of death in this survey. Current or former smoking, along with older age, previous heart disease, and male gender, independently predicted myocardial infarction in DAD.[77]

If heart disease has yet to vault into the first rank of mortality concerns among HIV clinicians, the growing myocardial infarction risk over time in the French study[76] and DAD,[77] along with an aging HIV population in Western countries, raises the odds that cardiovascular complications will climb up the concern list in this decade. In Fichtenbaum's managed care database population,[78] heart disease already sends more HIV-infected people to the hospital than liver disease, kidney disease, or opportunistic infection. In fact, significantly more people checked into the hospital with heart problems than with liver complications ($P < 0.05$). Only nonopportunistic infections beat cardiovascular disease in this hospital admission contest.

At London's Chelsea and Westminster Hospital, Moyle figures that heart disease causes one in 20 deaths among people with HIV. He tries to stick to National Cholesterol Education Program (NCEP) guidelines[79] in managing high lipids, a task that "may involve earlier switching approaches, most notably away from Kaletra." Fehmida Visnegarwala (Baylor College of Medicine) made a similar point from her clinic in Houston, writing that "cardiovascular causes [of death] can be prevented with careful patient education at the start of HAART therapy and avoiding drugs such as the boosted protease inhibitors as a first-line option among those with an elevated cardiovascular risk." At Washington University in St. Louis, Aberg worries about ischemia, cardiomyopathy, and arrhythmias in the cocaine abusers she treats.

Dabbling in HIV medicine, dabbling in death

Seven of the 29 clinicians who answered the *IAPAC Monthly* survey listed "care by clinicians with limited HIV experience" as a leading contributor to deaths in their clinic. Although most survey respondents did not see meager experience as an immediate cause of death, clearly it can contribute to any of the other causes listed in Table 1. Several studies back that impression statistically.

Before the arrival of potent antiretrovirals, a landmark study of 403 men who got an AIDS diagnosis from 1984 through mid-1994 found that those treated by physicians with more HIV experience lived longer.[10] After controlling for severity of illness and year of diagnosis, researchers at the University of Washington in Seattle determined that men cared for by clinicians with the most HIV experience had a 31 percent lower risk of death than men seen by clinicians with the least experience ($P < 0.02$).

Putting more powerful drugs into inexperienced clinicians' hands didn't solve this problem. Indeed, it may have made things worse by fueling the evolution of drug-resistant virus. In Germany, Mauss told *IAPAC Monthly* he has seen "a number of patients showing up with full-blown AIDS and no antiretroviral options left due to long-term treatment with failing regimens by ignorant or inexperienced physicians."

The daunting task of interpreting resistance tests contributes to this poor care, according to Kuritzkes. "I think we're beginning to plateau with resistance testing," he explained, "in just how well we can reach and educate providers who are very busy doing general medicine as well as some HIV care." These physicians typically "are unable to get to HIV meetings, don't have time to read

Ways to keep heart deaths a distant threat:
Consult the AIDS Clinical Trials Group (ACTG) Cardiovascular Subcommittee advice on preventing or controlling lipid elevations,[80] briefly:

- *Count the number of heart disease risk factors that modify the NCEP's low-density lipoprotein cholesterol (LDL-C) goals. The risk factors are (1) cigarette smoking, (2) systolic blood pressure of 140 mm HG or higher, or treatment with antihypertensives, (3) LDL-C below 40 mg/dL, (4) coronary heart disease in a first-degree male relative under 55 years old or a first-degree female relative under 65 years old, and (5) age over 45 years for men and over 55 years for women.*
- *If a person has two or more risk factors, estimate the 10-year risk of myocardial infarction or cardiac death with an online risk assessment tool (http://hin.nhlbi.nih.gov/atpiii/calculator.asp).*
- *After determining the risk category, identify LDL-C goals with the following table:*

		LDL-C level (mg/dL)	
Risk category	*Goal*	*Initiate therapeutic lifestyle change*	*Consider drug therapy*
CHD or risk equivalent	<100	≥100	≥130*
2 or more risk factors and 10-year risk of 10% to 20%	<130	≥130	≥130
2 or more risk factors and 10-year risk less than 10%	<130	≥130	≥160
0 to 1 risk factors	<160	≥160	≥190†

CHD = coronary heart disease.
*For LDL-C of 100 to 129 mg/dL, drug therapy is optional; consider treating HDL-C and triglyceride disorders.
†For an LDL-C of 160 to 189 mg/dL, drug therapy is optional.

Then:

- *Address modifiable risk factors such as diet and smoking.*
- *If lipids remain above threshold levels (see table above) "despite vigorous lifestyle interventions, consider altering antiretroviral therapy or lipid-lowering drugs."*
- *If lipid-lowering drugs are necessary, and if LDL-C is above the threshold or triglycerides measure 200 to 500 mg/dL with elevated non-high-density lipoprotein cholesterol, consider pravastatin or atorvastatin.*
- *If lipid-lowering drugs are necessary, and if triglycerides are above 500 mg/dL, consider gemfibrozil or fenofibrate.*

The ACTG's advice on "altering antiretroviral therapy" might now include a switch to ATV, which does not elevate lipids.

and develop a deep understanding of resistance testing, and they write a large number of prescriptions."

A survey of clinicians attending an HIV symposium in New York City disclosed a dismal grasp of basic resistance principles,[81] even though one might assume that physicians paying to hear HIV talks would have more than a glimmer of resistance savvy. A similar survey at another symposium two years later showed only modest improvement.[82] Although 57 percent of respondents claimed to have "moderate to high expertise" in treating HIV infection and 22 percent rated themselves HIV "experts," only 43 percent could name a mutation that caused resistance to five of seven antiretroviral groups, and 27 percent failed to make a correct match in every category.

So it's no surprise that a more recent study of physicians' HIV experience by the University of Washington group again linked less experience to worse survival odds.[12] Among HIV-infected people cared for at a large health maintenance organization from 1990 through 1999, those who saw physicians with the least HIV experience got the lowest level of outpatient pharmacy and laboratory services ($P < 0.001$) and were half as likely to visit a specialist ($P < 0.05$) as people seeing a physician with moderate or more HIV experience. And the people who got low-level services were 15 times more likely to die during the course of the study ($P = 0.02$). In British Columbia, a province with universal access to antiretrovirals, a study of 1,282 antiretroviral-naive people starting triple therapy between August 1996 and December 1999 found that every additional 100 HIV patients in a clinician's practice lowered the risk of death by almost 25 percent ($P = 0.037$).[9]

In some parts of the United States, particularly rural areas, people with HIV have to travel far to find a top HIV clinic. Many don't make the trip. In Colorado, Kuritzkes told *IAPAC Monthly*, HIV savvy ran thin outside a few urban centers. As a stopgap, every week one of his colleagues at the University of Colorado "would fly out to Grand Junction to hold HIV rounds with people who were holding down the fort for the rest of the week." Even when people live near seasoned HIV practitioners, he added, they can remain "stubbornly loyal to physicians who are well meaning but not well qualified."

Treatment by physicians with scant HIV skills is a tough problem to solve, but there are ways. One, suggested Gallant from Johns Hopkins, is to set a consistent policy. "Lack of care by experts needs to be addressed nationally," he wrote in responding to the *IAPAC Monthly* survey. "On the one hand the government says (in the DHHS guidelines[48]) that HIV care should be managed by experts. On the other hand we spend lots of money (through [the Health Resources Service Administration]) funding programs to teach generalists how to dabble in HIV. We need to get a consistent message out that HIV care should be managed (or at least co-managed) by experts." Putting pressure on third-party payers and managed care organizations, which often resist expert consultations, and educating people with HIV to insist on expert care would also pay dividends, Gallant added.

Several physicians' groups in the United States—including the HIV Medicine Association (HIVMA) and International Association of Physicians in AIDS Care (IAPAC)—are trying to set standards that earmark experts in HIV care. The HIVMA and IAPAC are working together with the American Board of Internal Medicine and other boards to develop a Certificate of Added Qualification that will identify clinicians expert in HIV medicine. Kuritzkes, now HIVMA's vice chairman, said his group also helps develop "training pathways for people who are not doing infectious disease fellowships and want to do HIV care."

German HIV mavens devised a way to address shortcomings in physicians' drug resistance knowledge. The Radata Project now embraces 59 HIV centers and 15 laboratories that collaborate to collate clinical data, resistance test and therapeutic drug monitoring results, and patient self-reports in an Internet database.[83,84] Physicians treating people with HIV and considering a regimen switch may contact Radata to get advice from two independent experts. That patient's data must be submitted to the database. At last year's 9th European AIDS Conference, Radata members reported that clinicians have sought switch advice 663 times for 193 people so far.[83]

How to help plug the experience gap:

- *Support efforts by the HIV Medicine Association (www.hivma.com) and the International Association of Physicians in AIDS Care (www.iapac.org) to establish qualifying standards for HIV clinicians.*
- *Encourage clinicians with modest HIV experience to refer infected people to HIV experts, either for ongoing primary care or for periodic consultation.*
- *Consider collaborations like the Radata Project (www.radata.de) to give clinicians expert advice on resistance and other issues.*
- *Educate people with HIV about the importance of expert care for HIV infection and give them information on how to advocate for their own healthcare.*

In reviewing a draft of this article, Sherer stressed the need "for ongoing mentoring and consultation as an integral part of an HIV care system. HIV medicine has become so much more complex that ongoing training updates and access to real-time consultations are important adjuncts to care for any HIV clinician, including the so-called experts."

. . . and all those other reasons

So far this review has considered the seven leading causes of death in HIV-infected people with access to antiretrovirals, as judged by a panel of 29 HIV clinicians. But other

mortal threats abound. A literature review suggested 12 other prime causes of death in people with HIV, and at least two survey respondents voted for each of them (Table 1). In Providence, Rhode Island, Charles Carpenter (Brown University) is "most concerned about the high rates of renal failure, mostly in African Americans." In Chicago, Sherer has seen suicides and deaths resulting from domestic violence, especially involving women and gay teens.

Some physicians who answered the *IAPAC Monthly* survey cited emerging causes of death that have received little or no attention in the literature. "We've seen several cases of fatal pulmonary embolism in the setting of what appears to be a hypercoagulable state," Zolopa wrote from Stanford. "Whether this is drug related or disease related is unclear." In Los Angeles, Peter Ruane (Tower Infectious Diseases Medical Associates) has come across a growing number of fatal atypical cytomegalovirus infections and invasive aspergillosis.

Meanwhile, the grisly opportunistic infections that quickly killed thousands in the years before effective prophylaxis and potent antiretrovirals have not gone away. A chart review comparing causes of death in 1995 and 1999-2000 at Parkland Memorial Hospital in Dallas counted 21 deaths from PCP in the first period (19 percent) and 15 in the second (17 percent).[7] In 1995, 77 people (69 percent) had taken PCP prophylaxis, compared with 44 (50 percent) in 1999-2000 ($P < 0.01$). The authors note that poor antiretroviral adherence appeared to correlate with poor prophylaxis adherence in the needy minority population that the hospital serves.

A few clinicians reminded *IAPAC Monthly* that antiretrovirals themselves can be the proximate cause of death. From Madrid, Arribas wrote that "we had a death caused by an interaction between lopinavir/ritonavir [LPV/RTV] and an ergot derivative." From Chicago, Sherer related the case of a man in another city who had been taking efavirenz for one week, became psychotic, and during a visit to his clinician threw himself from the eighth-floor office window.

Lactic acidosis was the most commonly cited antiretroviral toxicity in the *IAPAC Monthly* survey. Despite the growing attention this fatal complication has earned in the past several years, the symptoms sometimes still go unaddressed until it's too late. From Houston, Visnegarwala reported the case of a 37-year-old woman taking nelfinavir (NFV), d4T, and 3TC. Nonspecific abdominal pain led to two months of treatment for "fibroid disease." When first seen at Visnegarwala's clinic, the woman suffered from weight loss, shortness of breath, and a lactate level of 8.0 mmol/L. Despite intensive care including dialysis, intravenous carnitine, and multivitamin infusion, she died.

Although treatment guidelines typically do not recommend routine lactate monitoring, some HIV clinicians have taken up the practice, including Moyle in London. He e-mailed *IAPAC Monthly* that "serial monitoring may provide early pick-up of some events."

Yet no one doubts that, properly used, the potent antiretrovirals now available have saved far more lives than they threaten. Last year saw the licensing of five new antiretrovirals in the United States, including agents that are easier to take (fosamprenavir, NFV 625 mg, ATV), sometimes less toxic (ATV, fosamprenavir, FTC), and target a different step in the viral life cycle (enfuvirtide [ENF]).

Even in people with advanced disease, combinations of some new and some old drugs can still turn the tables on HIV. But first the drugs have to be prescribed, then they have to be taken. EuroSIDA researchers traced a steady correlation between treatment with more drugs and a lower risk of progression or death in 1,106 people with CD4 counts under 50 cells/mm^3.[85] Compared with people taking five drugs, the risk grew progressively greater in people taking four, three, two, and no drugs. Earlier research by EuroSIDA workers showed that continuing a PI regimen, even in people with fewer than 50 cells/mm^3, cut the risk of progression 43 percent compared with not taking a PI when the CD4 count falls that low.[86]

More recent work by the 13-cohort PLATO collaboration showed that CD4 counts continued to climb in people with triple-class failure as long as their viral load stayed below 10,000 copies/mL or 2 logs below the pretreatment setpoint.[87] Even in people with no apparent virologic suppression from continued therapy, the CD4 count dropped more slowly than it did in people who abandoned treatment. Further research by the PLATO group found a 3-fold higher risk of death in people with triple-class failure if their CD4 count fell below 200 cells/mm^3 and a 16-fold higher risk if it fell below 50 cells/mm^3.[88] Not taking antiretrovirals independently raised the risk of death 2.85 times.

On the other hand, a 1996-1999 survey by University of British Columbia researchers correlated intermittent use of triple therapy (judged by pharmacy records) in the first year of treatment with a 2.9 times higher risk of death ($P < 0.001$).[9]

What can new regimens do for people with advanced infection and a record of treatment failures? From Toronto, Mona Loutfy (University of Toronto) sketched the case of a person with multidrug-resistant virus and a CD4 count below 50 cells/mm^3 who started LPV/RTV, APV, ddI, 3TC, TDF, and T-20. The T-cell count climbed above 400 cells/mm^3 and the viral load sank below 50 copies/mL. But the patient died of a cocaine overdose.

In London, Youle saw a 25-year-old who never could stomach antiretrovirals for more than six weeks, suffering from nausea, diarrhea, and mental health problems. His T-cell tally stood at 22 cells/mm^3 and his viral load at 300,000 copies/mL. Eight weeks after starting ATV/RTV plus TDF and ddI, his viral load has dropped 2 logs, he feels no side effects, "and seems to be keen to continue."

Cases like these make an obvious point: Don't give up on people with advanced disease—and don't let them give up on themselves. A page from Aberg's casebook offers one more example:

A 25-year-old woman infected since she was 17 years old had a CD4 count of 99 cells/mm^3 and difficulty adhering to any regimen. Cervical dysplasia, oral candidiasis,

and bacterial pneumonia complicated her course. In March 2000, her clinicians diagnosed toxoplasmosis and central nervous system lymphoma. She took drugs for the toxo for two months but refused radiation therapy and all other medications.

Finally, she gave up and started planning her funeral. But she kept her medical appointments. In September 2000, she met another patient in the waiting room of Aberg's clinic, fell in love, and decided to give antiretrovirals another try. Her brain lesions resolved, her viral load has been out of sight since December 2000, her CD4 count now tops 800 cells/mm^3, and she delivered a healthy baby boy in August 2002. ■

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Acknowledgments

Thanks to Renslow Sherer (University of Chicago Hospitals) for reviewing this article, to Joel Gallant (Johns Hopkins University, Baltimore) and Bernard Hirschel (University Hospital, Geneva) for extensive comments, and to Daniel Kuritzkes (Brigham and Women's Hospital, Boston) and Alan Landay (Rush Presbyterian-St. Luke's Medical Center, Chicago) for interviews. Fabrice Bonnet (Saint-André Hospital, Bordeaux, France), Mardge Cohen (Cook County Hospital, Chicago), Joel Palefsky (University of California, San Francisco), and Richard Selik (US Centers for Disease Control and Prevention, Atlanta) provided reprints.

The following clinicians responded to the survey: Judith Aberg (Washington University, St. Louis, Missouri), José Arribas (Hospital La Paz, Madrid), Pedro Cahn (Fundación Huesped, Buenos Aires), Charles Carpenter (Brown University, Providence, Rhode Island), Bonaventura Clotet (Fundacio IRSI Caixa, Barcelona, Spain), Carl Fichtenbaum (University of Cincinnati), Joel Gallant (Johns Hopkins University, Baltimore, Maryland), Bernard Hirschel (University Hospital Geneva), Dushyantha Jayaweera (University of Miami), Philip Keiser (University of Texas Southwestern Medical School, Dallas), Daniel Kuritzkes (Brigham and Women's Hospital, Boston), Mona Loutfy (University of Toronto), Franco Maggiolo (Ospedali Riuniti, Bergamo, Italy), Josep Mallolas (University of Barcelona, Spain), Roberto Manfredi (University of Bologna "Alma Mater Studiorum"), W. Christopher Mathews (University of California, San Diego), Stefan Mauss (Center for HIV and Hepatogastroenterology, Düsseldorf, Germany), Graeme Moyle (Chelsea and Westminster Hospital, London), Ronald Reisler (University of Maryland, Baltimore), Peter Reiss (Academic Medical Center, Amsterdam), Douglas Richman (University of California, San Diego), William Rodriguez (Brigham and Women's Hospital, Boston), Peter Ruane (Tower Infectious Diseases Medical Associates, Los Angeles), Jonathan Schapiro (Sheba Medical Center, Tel Aviv), Renslow Sherer (University of Chicago Hospitals), Nancy Shulman (Stanford University, Stanford, California), Fehmida Visnegarwala (Baylor College of Medicine, Houston), Mike Youle (Royal Free Hospital, London), Andrew Zolopa (Stanford University, Stanford, California).

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ABSTRACTS

HIV Medicine

Determinants of long-term highly active antiretroviral treatment efficacy

Manegold C et al.

OBJECTIVES: Predictors of the efficacy of highly active antiretroviral therapy (HAART) have been investigated in several studies. To increase current knowledge, the study aimed to acquire comprehensive data over an extended observation time, to obtain information on possible performance differences among individual drugs, and to identify factors with influence on the initial response to a HAART regimen and the sustainability of the response. *METHODS:* The data were obtained from a prospective, single University Medical School HIV cohort. Clinical, laboratory, and treatment parameters for 475 patients were collected over 4.5 years. HAART efficacy was determined by analysis of variance and multivariate survival analysis. *RESULTS:* The overall initial complete response (CR) (<500 HIV-1 RNA copies/mL) was 76.3 percent. Use of indinavir [odds ratio (OR)=2.747, P=0.0009] and the number of new nucleoside reverse transcriptase inhibitors (NRTIs) (OR=1.862, P=0.0017) were positively associated with CR, while initial peripheral blood HIV RNA concentration (OR=0.383, P<0.0001), use of saquinavir hard gel capsules (OR=0.531, P=0.0302), the number of successive HAART regimens (OR=0.631, P<0.0001), and the number of previously used NRTIs (OR=0.728, P=0.0081) were negatively associated with CR. Sustainability of CR was positively correlated with use of indinavir [hazard ratio of relapse (HR)=0.255, P<0.0001] and hemoglobin levels (HR=0.873, P=0.0124), but negatively correlated with initial HIV RNA concentration (HR=1.273, P=0.0003) and the number of previously used NRTIs (HR=1.587, P<0.0001). A higher number of consecutive HAART regimens was associated with a markedly reduced CR, but with only a slightly higher risk of relapse. *CONCLUSIONS:* The initial response to HAART, as well as long-term efficacy, depends strongly on a few fundamental parameters that can easily be assessed in a clinical setting. There is a need for effective suppression of HIV replication over decades, and these factors should be considered early in treatment planning to identify patients with an unfavorable profile of risk factors for treatment failure.

HIV Med 2004;5(1):40-9.

American Journal of Psychiatry

The effect of previous alcohol abuse on cognitive function in HIV infection

Green JE et al.

OBJECTIVE: The authors' goal was to study the potential effect on cognitive function of an interaction of HIV infection and a history of alcohol abuse. *METHOD:* The subjects were 30 HIV-negative and 50 HIV-positive men with and without a past history of alcohol abuse. Thirty-three of the men (12 HIV negative and 21 HIV positive) had a past history of alcohol abuse, and 47 (18 HIV negative and 29 HIV positive) had never abused alcohol. Each subject's history of alcohol use was obtained by using a syndromal approach based on the Structured Clinical Interview for DSM-III-R and a quantitative approach. Each subject was given a battery of neuropsychological tests assessing verbal reasoning, reaction time, intelligence, memory, and dexterity. The subjects were then compared on a summary neuropsychological impairment rating. *RESULTS:* There were no significant differences in CD4 level, age, education, depression, anxiety, or other drug abuse history between the HIV-positive and HIV-negative groups with and without a history of alcohol abuse. Significant effects on cognitive function were found for past alcohol abuse and HIV infection, with significant interactions in verbal reasoning, auditory processing, and reaction time. This demonstrates that HIV infection and a history of alcohol abuse have independent effects on some aspects of higher cognitive function but may have synergistic effects on other cognitive domains. In the HIV-negative subjects there were no differences in cognitive function between subjects with and without a history of alcohol abuse. Among the HIV-positive subjects, those with a history of alcohol abuse performed more poorly on tests of verbal IQ, verbal reasoning, and reaction time. *CONCLUSIONS:* There are both additive and interactive effects of previous alcohol abuse and HIV infection on cognition. Individuals with a history of past alcohol abuse may be at greater risk for cognitive dysfunction in the context of HIV infection.

Am J Psychiatry 2004;161(2):249-54.

Sexually Transmitted Diseases

High prevalence of anal squamous intraepithelial lesions in HIV-positive men despite the use of highly active antiretroviral therapy

Piketty C et al.

BACKGROUND: The impact of highly active antiretroviral therapy (HAART) on the natural history of HPV infection and anal squamous intraepithelial lesions (SIL) in HIV-infected men who have sex with men (MSM) is poorly documented. *GOAL:* The goal of this study was to evaluate the prevalence of anal HPV infection and SIL in patients under HAART. *STUDY DESIGN:* Forty-five HIV-infected protease inhibitor-experienced MSM were enrolled in a cross-sectional study. Each patient provided anal samples for anal cytology, histology, and human papillomavirus (HPV) DNA testing. *RESULTS:* The patients had previously received HAART for a median of 32 months. Anal cytology was abnormal in 32 of 45 (71 percent) patients, including high-grade SIL in 10 patients (22 percent), low-grade SIL in 19 patients (42 percent), and atypical squamous cells of undetermined significance in three patients (7 percent). HPV DNA was detected in 36/45 men (80 percent). The prevalence of anal SIL and HPV infection was similar in patients exhibiting a significant increase in CD4 cell count after HAART initiation compared with those who did not. *CONCLUSION:* Our results demonstrate a high prevalence of anal SIL, including high-grade SIL, and anal HPV infection in HIV-infected MSM despite immune restoration under HAART.

Sex Transm Dis 2004;31(2):96-99.

Atherosclerosis

Fenofibrate improves the atherogenic lipid profile and enhances LDL resistance to oxidation in HIV-positive adults

Badiou S et al.

BACKGROUND: Low HDL-cholesterol, hypertriglyceridemia (HTG) and occurrence of small dense LDL could be involved in increased cardiovascular risk in HIV-infected patients. This study evaluates the effects of fenofibrate and/or Vitamin E on lipoprotein profile. *DESIGN:* Thirty-six HIV-positive adults with fasting triglycerides (TGs) = 2 mmol/l and stable antiretroviral therapy (ART) were randomly assigned to receive either micronised fenofibrate (200 mg/day) or Vitamin E (500 mg/day) for a first period of three months and the association of both for an additional three-month period. *METHODS AND RESULTS:* Total cholesterol, HDL-C, LDL-C, triglycerides, apoA1, apoB, apoCIII, lipoprotein composition, LDL size and LDL resistance to copper-induced oxidation were determined before initiation of fenofibrate or Vitamin E, and three and six months thereafter. Three months of fenofibrate treatment results in a significant decrease in triglycerides (-40 percent), apoCIII (-21 percent), total cholesterol (-14 percent), apoB (-17 percent) levels, non-HDL-C (-17 percent), TG/apoA1 ratio in HDL (-27 percent) associated with an increase in HDL-C (+15 percent) and apoA1 (+11 percent) levels. Moreover, fenofibrate increases LDL size and enhances LDL resistance to oxidation. Three months of Vitamin E supplementation only improves LDL resistance to oxidation and addition to fenofibrate results in a slightly greater effect. *CONCLUSION:* Fenofibrate therapy improves the atherogenic lipid profile in HIV-positive adults with hypertriglyceridemia.

Atherosclerosis 2004;172(2):273-279.

Updated HIV/HCV coinfection consensus guidelines

Expert information regarding the best care for patients who are coinfected with HIV and hepatitis C virus (HCV) is lacking and few trials have addressed the unique treatment and management requirements of this population. In an effort to build a standard of care that incorporates the latest study results for this group of patients, an international group of clinicians and researchers have formulated new consensus guidelines entitled, "Care of Patients with Hepatitis C and HIV Coinfection: Recommendations from the HIV-HCV International Panel."

Table 1. **Response to peginterferon plus ribavirin in HIV/HCV-coinfected patients**

Study	No.	Negative HCV-RNA at 12-24 weeks %	SR %	HCV-1/4 response %	HCV-2/3 response %	Discontinuation because of side effects %
Goelz *et al.* (56)	25	36	20	?	?	32
Pérez-Olmeda *et al.* (57)	68	50	35	24	52	15
Rockstroh *et al.* (58)	55	46	27	19?	60?	20
Perronne *et al.* (59)	100	?	38	25	42	28
Hopkins *et al.* (60)	16	45	?	0	62	6
Chung *et al.* (61)	133	44	?	33	80	?
Cargnel *et al.* (62)	32	56	34	20	80	25

Introduction

Liver disease caused by chronic HCV infection is now a leading cause of morbidity and mortality among HIV-infected patients in the developed world, where classic opportunistic complications of severe immunodeficiency have declined dramatically as a result of the widespread use of potent antiretroviral therapies.

The newly released updated consensus guidelines grew out of a series of meetings of an HIV-HCV International Panel of nine experts in the field of HIV and viral hepatitis, which tackled nine questions of clinical importance. Answers to those nine questions form the basis for the consensus guidelines published in January 2004. Following in excerpt format are the nine questions and subsequent answers contained in the consensus guidelines.

What is the influence of HCV on HIV disease progression and response to antiretroviral therapy?

Panel recommendation: HCV might act as a co-factor for HIV disease progression by several mechanisms. First, unspecific immune stimulation driven by chronic HCV infection might enhance HIV replication. Second, the infection of immune cells by HCV could favor CD4 T-cell depletion and partly blunt the immune recovery that follows successful antiretroviral therapy. Third, HCV could compromise the benefit of antiretroviral drugs as a result of a higher incidence of liver toxicity and treatment discontinuation. However, a negative impact of HCV on HIV disease progression has not been recognized in some large clinical epidemiological studies (Table 1).

Who are candidates for anti-HCV treatment?

Panel recommendation: All HIV-infected individuals should be screened for HCV antibodies. Those with positive HCV serology should be tested for HCV-RNA. Individuals with positive HCV-RNA should be considered as candidates for anti-HCV treatment.

A plasma HCV load and genotyping should be requested before initiating therapy. Treatment should be provided to patients with repeated elevated alanine aminotransferase levels, CD4 counts greater than 350 cells/µl, relatively low plasma HIV-RNA levels (eg, less than 50,000 copies/ml), no active consumption of illegal drugs or high alcohol intake, and no previous severe neuropsychiatric conditions.

Treatment in patients with normal alanine aminotransferase levels should be carried out in the context of study protocols or when a liver biopsy has proved the presence of clinically significant fibrosis (eg, F2 or above). Treatment in patients with CD4 counts below 350 cells/µl should be prescribed cautiously. The treatment of choice is the combination of pegylated interferon (peg-IFN) plus ribavirin.

What is the role of pre-treatment liver biopsy?

Panel recommendation: The role of liver biopsy for treatment decision purposes is controversial in HIV-HCV-coinfected patients. The patients' reluctance to accept it or other difficulties should not defer the prescription of anti-HCV therapy once it is considered appropriate, given the faster progression to end-stage liver disease in coinfected patients. When the histological information is available for patients with HCV genotypes 1 or 4, treatment could be deferred if there is no fibrosis (F0), or in patients with F1 willing to accept a second follow-up liver biopsy. In patients with normal transaminase levels, liver biopsy should be performed before prescribing therapy.

How should HIV-positive patients with chronic HCV be treated?

Panel recommendation: The overall response to anti-HCV therapy is lower in patients coinfected with HIV. Sustained response rates of 40 percent to 60 percent are seen in patients with HCV genotypes 2 or 3, but lower than 25 percent in those with HCV genotypes 1 or 4. Both early virological responses and relapses are less and more frequent, respectively, in coinfected patients compared with HCV-monoinfected individuals.

The benefit of extending therapy (more than six months for HCV genotypes 2 or 3; and more than 12 months for HCV genotypes 1 or 4) in early virological

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responders should be examined in clinical trials. Moreover, treatment adherence should be considered a critical factor for the attainment of response and must be encouraged actively over the whole treatment period.

How should the response to anti-HCV therapy in HIV-positive patients be monitored?
Panel recommendation: Early virological response to anti-HCV therapy predicts the chance of sustained response in HIV-coinfected patients as it does in HCV-monoinfected individuals. Moreover, the use of an early time-point for treatment decision making seems to be equally appropriate in coinfected patients. Only patients showing a decline in serum HCV-RNA levels greater than 2 logs at 12 weeks on therapy will have a chance of reaching a sustained response. Therefore, treatment might be discontinued in the rest. This is of particular relevance, given the concern about the risk of toxicity derived from interactions between anti-HCV therapy and antiretroviral drugs.

How should adverse effects of anti-HCV therapy be managed in HIV-positive patients?
Panel recommendation: In the majority of cases, anti-HCV therapy causes side effects such as fever, malaise, asthenia, and depression. Patients should be informed in advance about these side effects and how to prevent and manage them (eg, paracetamol for influenza-like symptoms). The treatment of depression should be considered as soon as symptoms begin to develop. Peg-IFN may produce significant CD4 count declines and neutropenia, which are reversible after discontinuing the drug. Ribavirin may cause anemia within the first 12 weeks of therapy. Doctors should improve their expertise in the management of these side effects, trying to keep patients on therapy as long as no serious toxicities develop.

How can the toxicity caused by interactions between anti-HIV drugs and anti-HCV therapy be avoided?
Panel recommendation: Interactions between antiretroviral drugs and ribavirin may be harmful. Given the higher risk of pancreatitis and lactic acidosis in all treated patients as well as of liver decompensation in cirrhotic individuals, didanosine (ddI) should be avoided when taking ribavirin. On the other hand, zidovudine (ZDV) should be used with caution when ribavirin is given, because both may produce anemia. Patients should be advised of the possibility of experiencing severe weight loss, mimicking a rapid progression of lipoatrophy, probably as a result of a potentiation of mitochondrial damage in the subcutaneous fat tissue caused by taking ribavirin and some nucleoside reverse transcriptase inhibitors (NRTIs).

What anti-HIV drugs are associated with hepatotoxicity?
Panel recommendation: Liver enzyme elevations after beginning antiretroviral therapy are more frequent in patients with underlying chronic hepatitis B and C. Therefore drugs with more hepatotoxic profiles—for example, nevirapine (NVP) and ritonavir (RTV)—should be used cautiously in coinfected patients. Treatment should be discontinued in patients with symptoms or grade 4 increases in aminotransferase levels.

In certain cases, immune reconstitution phenomena may lead to increases in transaminase levels after starting potent anti-HIV therapy. The close monitoring of these patients during the first weeks may enable them to remain on therapy, because they experience a progressive resolution of liver abnormalities without discontinuing treatment.

Who are candidates and what is the prognosis for HIV/HCV-coinfected patients requiring liver transplantation?
Panel recommendation: All HIV-infected patients with end-stage liver disease as a result of HCV should be considered as candidates for liver transplantation as long as they do not have advanced HIV disease. In those with severe immunodeficiency (less than 100 cells/µl), the control of HIV replication and immune restoration should be prioritized.

The evaluation and the pre- and post-operative medical management of HIV-positive candidates for OLT must be performed by an interdisciplinary team composed of a hepatologist, infectious disease specialist, surgeons, psychologists, social workers, and members of alcohol, heroin and cocaine detoxification programs.

HIV-positive candidates should have CD4 counts greater than 100 cells/µl and plasma HIV RNA levels below 200 copies/ml, or the chance of becoming undetectable using optional drugs for successful treatment after transplantation. Moreover, they should have abstained from the consumption of alcohol and illegal drugs for at least six months.

Patients with a good immunological response to antiretroviral therapy but a previous history of AIDS-related opportunistic infections or neoplasms (including Kaposi's sarcoma, cervical carcinomas, and anal squamous carcinomas) deserve special attention, given the potentially higher risk of relapses of those conditions using immunosuppressors. ■

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Frank Graziano

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

This month, *IAPAC Monthly* is proud to feature Frank Graziano, Professor of Medicine at the University of Wisconsin Hospitals and Clinics in Madison.

What proverb, colloquial expression, or quote best describes how you view the world and yourself in it?
Tomorrow could always be a better day!

What activities, avocations, of hobbies interest you?
Anything to do with exercise—especially running and biking.

If you could live anywhere in the world, where would it be?
Kampala, Uganda—they need so much compassion and help.

Who are your mentors or real life heroes?
My real life heroes are my family and friends—especially my wife who puts up with my long hours away—but still loves me.

With which historical figure do you most identify?
I've never given this much thought, but I hope I identify with any person (historical or not) who believes that perhaps they can make a difference in the life of one person who is sick—if they try hard enough.

Who are your favorite authors, painters, and/or composers?
John Grisham for his novels that continue to keep me entertained. Claude Monet, whose colors are candy for my eyes.

If you could have chosen to live during any time period in human history, which would it be?
When I grew up in the 1940s/1950s, I had such a great family—why trade it for something else?

If you did not have the option of becoming a physician, what would you have likely become, given the opportunity?
It's not altruistic, but I love sports and I always wanted to be a sports announcer.

In your opinion, what are the greatest achievements and failures of humanity?
The greatest achievement is all the natural beauty God created and we have the opportunity to use and enhance. The greatest failures are the ways in which we tend to tarnish all this God-created beauty.

What is your prediction as to the future of our planet one full decade from present day?
Optimistically, we have put in place the financial and human resources to treat AIDS in Africa. Pessimistically, we are embroiled in yet another useless war that takes the finances and human resources away from treating AIDS in Africa. I really want to be an optimist! ■

SAY ANYTHING

There's something nuts about holding out a begging bowl for an organization dedicated to confronting and subduing the AIDS pandemic.
Stephen Lewis, a Canadian diplomat and the United Nations' Special Envoy for AIDS in Africa, during a presentation delivered February 8, 2004, to more than 3,900 delegates attending the 11th Conference on Retroviruses and Opportunistic Infections (CROI) in San Francisco. Lewis argued that wealthy nations must make up for a "decade of financial abstinence" to battle the global AIDS pandemic. He stated that no country, including his own, is paying an adequate share toward the estimated need of US$3.6 billion in 2005 for the Global Fund to Fight AIDS, Tuberculosis, and Malaria.

The year-on-year increase we are observing... is a cause of considerable concern.
Barry Evans of Britain's Health Protection Agency (HPA) quoted in a February 12, 2004, Reuters report about how increases in unsafe sex have pushed HIV infection rates in Britain to what are expected to be their highest ever. According to the HPA, new HIV infections jumped 20 percent between 2002 and 2003 and are expected to continue increasing. New diagnoses among gay men are expected to rise to more than 2,000 this year, representing the greatest increase in any year since HIV testing became available in the late 1980s. The agency also reported a 27 percent increase in HIV infections among heterosexuals, but added that 80 percent of those cases involved immigrants who were infected in countries with a high prevalence of HIV.

Inside a hospital, there must be a policy for a doctor to disclose his HIV infection.
Andre Senikas, of the Quebec Medical Association, in a February 4, 2004, Canadian Press article reiterating the association's requirement that physicians disclose HIV status to their employers and work with an internal committee of colleagues and supervisors to ensure that their work can be carried out safely. A public debate on HIV-infected healthcare professionals erupted in January 2004 when Ste-Justine Hospital in Montreal disclosed that one of its surgeons had operated on more than 2,000 children over several years without hospital administrators knowing she is HIV-positive.

Without such measures to protect the health of young people abroad, already elevated rates of [sexually transmitted infections] and unwanted pregnancies in the United Kingdom may continue to climb, fueled by the mixture of media hype, substance use and opportunity associated with dance music tourists.
Mark Bellis of Liverpool's John Moores University quoted in a February 3, 2004, Reuters report about a study indicating that the sexual antics of 250,000 young British men and women who visit the Spanish tourist island of Ibiza each year could endanger their health. According to Bellis, who was the three-year study's lead author, 11 percent of 16- to 35-year-old males and 3 percent of females reported having sex with six or more people during a typical 10-day stay. Thirty-eight percent of study participants who claimed to have sex failed to use a condom.

Actress Emma Thompson and UNAIDS' Peter Piot at the launch of the Global Coalition of Women and AIDS.

The "ABC" slogan—Abstain, Be Faithful, Use a Condom—is the mainstay of many HIV prevention programs. But for too many women and girls, this message has no purchase. Where sexual violence is widespread, abstention or insisting on condom use is not a realistic option.
British actress and activist Emma Thompson and Joint United Nations Programme on HIV/AIDS (UNAIDS) Executive Director Peter Piot in a February 2, 2004, opinion piece for BBC News on-line. The two were instrumental in launching the Global Coalition on Women and AIDS, "which gathers activists, government representatives, celebrities, and community workers who are committed to improving the lives of women and girls," Piot and Thompson wrote. Sexual inequality, they argue, means that women are more susceptible to sexual assault, less able to take action to prevent their own HIV infection, and less able to procure care and treatment.

7th International Conference on Healthcare Resource Allocation for HIV/AIDS

HIV/AIDS and the United Nations Millennium Development Goals: Are We on Target?

November 3 - 4, 2004 - Washington, DC

Call for Abstracts

At the UN Millennium Summit in September 2000, world leaders placed sustainable development at the heart of the global agenda by adopting eight time-bound Millennium Development Goals (MDGs) that set clear targets for reducing poverty, hunger, disease, illiteracy, conflict, environmental degradation, and discrimination against women by 2015.

While the MDGs are highly intertwined and complementary, Goal 6 commits nations to specifically "combat HIV/AIDS, malaria, and other diseases." The UN Millennium Project—spearheaded by Jeffrey Sachs (Columbia University)—has identified ten priority areas through which to achieve Goal 6. Four years after the UN Millennium Summit, the 7th International Conference on Healthcare Resource Allocation for HIV/AIDS (7th ICHRA) aims to assess global responses to Goal 6 as well as our relative success in addressing the related ten priority areas.

IAPAC thus welcomes abstract submissions for the 7th ICHRA along the following ten tracks (representing the ten priority areas):

Track 1	Access to Treatment
Track 2	Health System Investment to Support HIV/AIDS Services
Track 3	Prevention of HIV Transmission
Track 4	HIV/AIDS and Vulnerable Populations
Track 5	Integration of HIV Prevention, Care, and Treatment Efforts
Track 6	Empowerment of Women to Combat HIV/AIDS
Track 7	Strategies to Address HIV/AIDS in Orphans and Vulnerable Populations
Track 8	Enhancing the United Nations Response
Track 9	Expanding and Improving Implementation of Domestic and International Funding for HIV/AIDS
Track 10	Empowerment of Governments and Measures for Accountability

Deadline for electronic abstract submission is August 4, 2004.

Visit www.iapac.org to submit your abstract(s) and/or for further information about the 7th ICHRA, abstract submission guidelines, and abstract review procedures.