

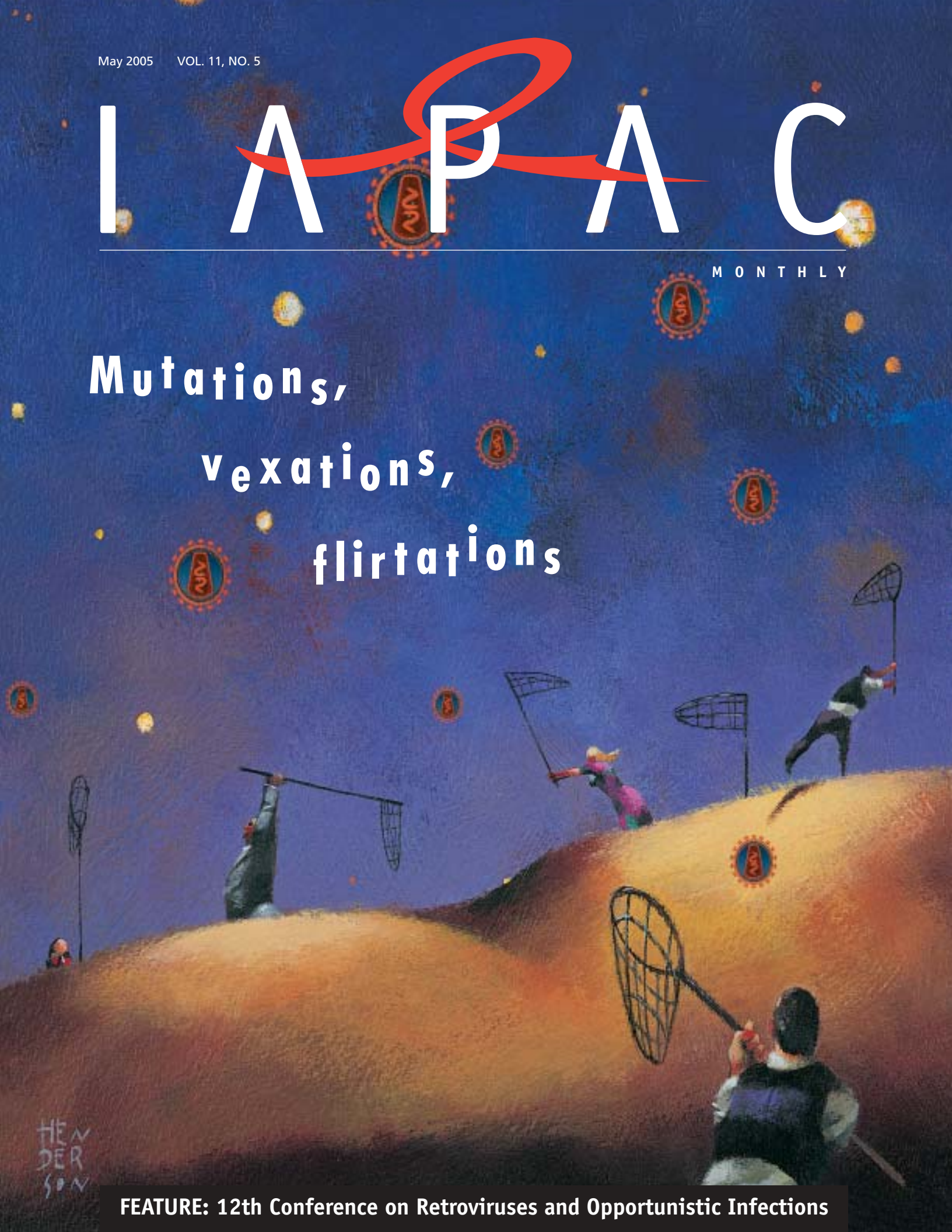
May 2005 VOL. 11, NO. 5

I A P A C



MONTHLY

**Mutations,
vexations,
flirtations**



HENDERSON

FEATURE: 12th Conference on Retroviruses and Opportunistic Infections

128



Mutations, vexations, flirtations

Mark Mascolini

This second installment in our review of the 12th Conference on Retroviruses and Opportunistic Infections probes studies on resistance after single-dose nevirapine and during chronic infection (the “mutations”), antiretroviral side effects (the “vexations”), and the gay epidemic in North America and Europe (the “flirtations”).

DEPARTMENTS

REPORT FROM THE PRESIDENT	120
TOP 10	122
ABSTRACTS	146
FOCUS ON HEPATITIS	147
IN THE LIFE	148
SAY ANYTHING	150



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

PRESIDENT/CEO José M. Zuniga
VICE PRESIDENT/CEC Brian Hujdich

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

EXECUTIVE DIRECTOR Nathalie C. Kaunda
DEPUTY DIRECTOR Jaz Hughes

IAPAC MONTHLY

EDITOR-IN-CHIEF José M. Zuniga
MANAGING EDITOR Lisa McKamy
CREATIVE/DESIGN DIRECTOR Holly J. Emanuelson
ADVERTISING DIRECTOR Cathy Córdova
WRITER-AT-LARGE Mark Mascolini
CONTRIBUTING WRITERS
Edwin J. Bernard, Michael Carter, Thomas D. Cook,
Chris Gadd, Amin Ghaziani, Carrie Scharrer

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.

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

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

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

IAPAC Monthly © 2005, International Association of Physicians in AIDS Care. Reproduction of any part without written permission is prohibited. The information contained in *IAPAC Monthly* shall not, in whole or in part, be redistributed, reproduced, or entered into a computer without permission.



R E P O R T F R O M T H E P R E S I D E N T

Morality politics

José M. Zuniga

I was forced to make a difficult decision in December 2004 when, in support of a proposal for rapidly scaling up access to antiretroviral therapy (ART) in three African countries through the US President's Emergency Plan for AIDS Relief (PEPFAR), the International Association of Physicians in AIDS Care (IAPAC) and seven partner organizations each were pressed to submit institutional statements pledging not to condone commercial sex work.

The decision was a difficult one from the perspective of weighing the needs of 109,500 Ethiopian, South African, and Tanzanian HIV-positive patients we hoped to place on ART versus appearing to condemn an entire group of people based solely on their profession. In the end we did so—a decision that has weighed on my conscience for the better part of a year—even though deep down I felt it was grossly unfair of the US government to ask institutions committed to social justice to violate the human rights of entire populations of at-risk individuals.

Brazil's government was also recently asked to make a choice: additional resources were forthcoming to advance its thus far successful battle against HIV/AIDS, but to receive them, the government must ensure that only a limited proportion of those resources would be allocated to non-governmental organizations (NGOs) working with commercial sex workers and other at-risk groups to stem the tide of new HIV infections. It did not take long for Brazil to reject US\$40 million in US Agency for International Development (USAID) funding meant to support that country's AIDS control program through 2008. In announcing his government's stance, Pedro Chequer, Director of Brazil's

National Program for Sexually Transmitted Diseases and AIDS, discarded the possibility of cooperation contracts between USAID and Brazilian NGOs, if these prohibit working with commercial sex workers.

"In no way [will] Brazil give up its established policy of allowing access to condoms, syringes, and needles. We will not permit that our NGOs be subject to foreign legislation in this sector," warned Chequer, immediately following a "friendly" meeting with USAID representatives meant to resolve a long-simmering impasse between São Paulo and Washington, DC. In rhetoric sure to infuriate the Bush Administration, he went on to state in a May 2, 2005, *Wall Street Journal* article that, "We can't control [the disease] with principles that are Manichean, theological, fundamentalist, and Shiite..."

The Bush Administration's hard line on commercial sex work dates back to the 2003 National Security Presidential Directive 22, which represents a zero tolerance policy for sexual trafficking of women and girls. The directive also requires that anti-trafficking funds be kept from groups that do not take an abolitionist approach to commercial sex work.

To be sure, a significant percentage of commercial sex work is a result of trafficking. And, because women and girls are more vulnerable to HIV disease because of political, social, and cultural inequality, those most at risk are those who are trafficked—coerced, forced, or tricked into commercial sex. As Holly Burkhalter of Physicians for Human Rights testified two years ago before the US House of Representatives' International Relations Committee during hearings to reauthorize the Victims of Trafficking and Violence Prevention Act of 2000:

"Sex trafficking is an almost inevitable death sentence for the victims for several

reasons. First, because they are virtually or literally enslaved, trafficking victims have no ability to insist upon condom use and are vulnerable to dangerous sexual practices most associated with transmission. Second, trafficking victims are forced to endure intercourse with multiple partners. And third, violence is common in commercial sex and particularly prevalent when women or children are forcibly subjected to sex against their will."

Yet, in stretching the presidential directive to the point of prohibiting US aid agencies from funding NGOs unless they publicly condemn commercial sex work (whether or not it is a direct result of organized sex trafficking), the US government is ensuring that the victims of societal neglect—600,000 to 800,000 through trafficking; millions through HIV infection—are denied their fundamental human right to health. Our inalienable right to our beliefs—religious or otherwise—must never be seen to trump other rights without which the human condition deteriorates.

Violence against and subordination of women (and men, whose sexual subordination is largely ignored) through trafficking are violations of human rights and, as such, every government has a moral obligation to halt these reprehensible practices. However, there will always be a need to balance the needs of the few with the needs of the many—in this case, the counterweight is reflected in the need to avoid creating a harsher environment for and denying the rights of an already stigmatized high-risk group of individuals who must not be discouraged from enjoying the benefit of HIV/AIDS prevention and care programs. ■

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

South African physician to lead IAPAC-AFRO

The International Association of Physicians in AIDS Care (IAPAC) has appointed Nathalie C. Kaunda, a South African HIV/AIDS-treating physician, to serve as Executive Director of its African Regional Office (IAPAC-AFRO) in Johannesburg. Kaunda's appointment is based on her academic and professional qualifications, as well as her demonstrated commitment to wage battle against the AIDS epidemic in Africa.

"I am delighted Dr. Kaunda has elected to continue her work for the benefit of Africans living with HIV/AIDS, and in the service of advancing our collective cause against the global AIDS pandemic, by leading IAPAC's efforts on the African continent," said IAPAC President/CEO José M. Zuniga.

Kaunda trained at the University of Zambia School of Medicine, and subsequently gained extensive clinical surgical experience in Britain and Zambia before moving to South Africa in 1997. Since 2004, she served as a medical officer in the Clinical HIV Research Unit of the Wits Health Consortium at the University of the Witwatersrand, where she worked with colleagues to scale up access to antiretroviral therapy at the Helen Joseph Hospital's Themba Lethu Clinic. ■



Nathalie C. Kaunda

An ounce of prevention



● ● ●

**Counsel your
HIV-positive
patients about
safer sex.
An ounce
of prevention
is worth
everyone's
effort!**



battling complacency
advancing commitment

1998



TOP 10

10 Most Important Developments in HIV Medicine



1. In Zambia, 1,300 teachers died in the first 10 months of 1998 due to HIV/AIDS; a number that represents approximately two thirds of the total number of all the new teachers trained in that country each year.
2. France's Supreme Court ruled that knowingly transmitting HIV could not be considered poisoning. According to the court, "Knowledge of the lethal potential of the substance administered alone is not enough proof of the intent to kill." The ruling makes it likely a former premier and two former ministers will not be prosecuted for the 1985 infection of 1,250 hemophiliacs by state-supplied blood products.
3. Researchers at the 12th International AIDS Conference present the first data about the ominous spread of an HIV strain that is resistant to protease inhibitors (PIs).
4. A report released by the United Nations Programme on HIV/AIDS (UNAIDS) suggests that AIDS is significantly lowering life expectancy rates on the African continent to levels not seen in Africa since the 1950s.



5. Study after study presented at the 5th Conference on Retroviruses and Opportunistic Infections (CROI) demonstrated that the first PI a patient takes has the best anti-HIV activity. Subsequent regimens, even those that contain one or more new PIs, are likely to be less effective, due to cross-resistance among currently available compounds.
6. UNAIDS reports that as of the end of 1998, more than 33 million people worldwide were living with HIV/AIDS, 43 percent of them female. An estimated 5.8 million new HIV infections occurred worldwide during 1998—approximately 16,000 new infections each day. More than 95 percent of these new infections occurred in developing countries.
7. The US Food and Drug Administration (FDA) approves a new nucleoside reverse transcriptase inhibitor (NRTI) as well as a new nonnucleoside reverse transcriptase inhibitor (NNRTI): abacavir (ABC) and efavirenz (EFV), respectively.



8. The South African government enacted legislation that would enable the country to override the patent rights of brand-name pharmaceutical companies by importing generic antiretroviral drugs from India and Thailand. Thirty-nine pharmaceutical companies sued the South African government on the grounds that the legislation violated international trade agreements.
9. A study of the French Perinatal Cohort published by Mandelbrot *et al* suggests that perinatal transmission of HIV from mother to child can be reduced to 1 percent by use of cesarian section and zidovudine (ZDV).
10. AIDS researcher and human rights pioneer Jonathan Mann (the first director of the United Nations' Global Programme on AIDS [GPA]) is killed in the crash of Swissair Flight 111. His wife, vaccinologist Mary Lou Clements-Mann, also perished in the air disaster.

References

1. Barks-Ruggles E. Meeting the global challenge of HIV/AIDS: Why the United States should act quickly. *Brookings Policy Brief* 2001;75:1-8.
2. CNN. French court rules HIV infection is not poisoning. July 2, 1998. <http://www.cnn.com/HEALTH/9807/02/aids.conf.wrap/> (Accessed May 6, 2005).
3. Perlman D. AIDS discovery worries scientists; S.F. man infected with drug-resistant strain of HIV. July 1, 1998. *San Francisco Chronicle*.

4. World Health Organization. AIDS not losing momentum—HIV has infected 50 million, killed 16 million, since epidemic began. Press Release. November 23, 1999.
5. Averitt D. Highlights of the 5th Conference on Retroviruses and Opportunistic Infections. *AIDS Care*. April 1998. <http://www.thebody.com/hivnews/aidscares/apr98/editor.html> (Accessed May 6, 2005).
6. Fauci AS. The AIDS epidemic—Considerations for the 21st century. *N Engl J Med* 1999;341(14):1046-1050.
7. US Food and Drug Administration (FDA). FDA approves abacavir for HIV-1 infection. FDA Talk Paper. December 18, 1998. <http://www.fda.gov/bbs/topics/ANSWERS/ANS00930.html> (Accessed May 6, 2005); FDA. FDA approves

- new drug to treat HIV, AIDS. *HHS News*. September 18, 1998. <http://www.fda.gov/bbs/topics/NEWS/NEW00654.html> (Accessed May 6, 2005).
8. Fleshman M. Drug price plunge energizes AIDS fight. *Africa Recovery* 2001;15(1-2):1.
9. Mandelbrot L, Le Chenadec J, Berrebi A. Perinatal HIV-1 transmission: interaction between zidovudine prophylaxis and mode of delivery in the French Perinatal Cohort. *JAMA* 1998;280(1):55-60.
10. British Broadcasting Corporation (BBC). No survivors in Canada air crash. September 3, 1998. <http://news.bbc.co.uk/1/hi/world/americas/163662.stm> (Accessed May 6, 2005).



**Mutations,
vexations,
flirtations**

Mark Mascolini

Nearly everything is right about the Conference on Retroviruses and Opportunistic Infections (CROI) except the official color. (Would you call that gallbladder green?) This midwinter conference routinely features fresh data from top teams, trenchant reviews by starry exegetes, and free coffee.

No matter what your precise interest in this field—antiretroviral pharmacology? ever-changeable epidemiology? devilish accessory genes?—you will probably find at least one slide session on that topic and serried ranks of worthy posters.

And like the slippery retrovirus it seeks to delimit, CROI keeps evolving. Originally called the “National Conference on Human Retroviruses,” CROI now hosts an international cast with a global (but strictly scientific) agenda. Especially in the last few years, the conference has offered a forum for research on HIV prevention and care in the epidemic’s far-flung epicenters.

The 12th CROI, held February 22-25, 2005, in Boston, paid special attention to prevention of mother-to-child transmission with that embattled nonnucleoside reverse transcriptase inhibitor (NNRTI), nevirapine (NVP). This second part of the *IAPAC Monthly’s* conference coverage also probes studies on resistance during chronic infection, antiretroviral side effects (the “vexations”), and the gay epidemic in North America and Europe (the “flirtations”).

NEVIRAPINE DE NOVO

In the archives of antiretroviral hagiography, no story has more deaths and resurrections than NVP’s. The past year featured this drug’s second or third crucifixion, this time for messy data handling in the landmark trial of single-dose NVP for perinatal prophylaxis—coupled with unhappy toxicity reports. That conjunction led to confused cries that evil Western drug lords had unleashed a baby killer in Africa.

In a perspicacious and palliative talk, James McIntyre (Chris Hani Baragwanath Hospital, Johannesburg) observed that a solitary dose of NVP does not cause liver failure [abstract 8]. No significant clinical or laboratory toxicities emerged in 4,429 women or 4,875 infants exposed to single-dose NVP in six trials, in addition to the much-bruited HIVNET 012.

The tragedy is not that so many pregnant women are taking this drug, McIntyre counseled, but that so few do. He estimated that about 3 percent of HIV-infected pregnant women who need NVP or other short-course antiretrovirals get them.

But a sole dose of NVP does breed resistant virus—probably in every infected woman who takes it. That judgment came from resistance savants Douglas Richman (University of California, San Diego) and François Clavel (Bichat-Claude Bernard Hospital, Paris). Slowly dwindling levels of this durable drug as HIV revs its replicating engine virtually guarantee that the virus will evolve the one or more mutations that can imperil responses to this drug—or efavirenz (EFV). Conventional assays may not spot this resistant virus, but supersensitive assays can, as three CROI studies showed:



Rife resistance after single-dose nevirapine

With Johannesburg colleagues, Jeffrey Johnson (US Centers for Disease Control and Prevention [CDC],

Atlanta) deployed a real-time polymerase

chain reaction (PCR) assay trained to ferret out the K103N NNRTI resistance mutation in subtype C virus, the prevalent subtype in a South African study of single-dose NVP [abstract 100]. The assay can dig up K103Ns comprising a mere 0.2 percent of a viral population, whereas standard nucleotide sequencing can't see virus making up less than 20 percent of a population.

Johnson focused on 50 women in whom neither standard sequencing nor real-time PCR spotted K103N before they took one dose of NVP. After treatment the standard assay sighted K103N in 10 of 50 samples, and the souped-up CDC assay confirmed that finding. But in the 40 samples with no hint of K103N on routine testing, PCR described the mutant in 16 (40 percent).

Next Johnson rolled out a real-time PCR probe aimed at the Y181C nonnucleotide mutation. With a population detection limit of 0.3 percent, the assay saw no Y181Cs before women took NVP. But in 46 women with no hint of Y181C on standard sequencing, real-time PCR picked it up in five (11 percent).

Searching plasma samples collected up to nine months after single-dose NVP, even Johnson's real-time PCR test couldn't see Y181C in six samples examined at three to six months or in five samples scoured at six to nine months. But K103N touched off the real-time PCR alarm in four of six samples surveyed at three to six months and in three of five at six to nine months.

Overall, Johnson figured that two thirds of women studied with real-time PCR had K103N or Y181C after single-dose NVP, a 62 percent jump from estimates with standard sequencing.

Reading an allele-specific PCR meter, Sarah Palmer (National Cancer Institute, Frederick, Maryland) confirmed that K103N and Y181C hang on for months after solo-dose NVP, even if routine sequencing can't spot them [abstract 101]. Palmer's analysis involved three groups of women enrolled in NVP prophylaxis trials—eight in whom standard sequencing saw resistant virus six weeks and six months after single-dose NVP but not at 12 months, 11 in whom the standard test registered resistant virus at six weeks but not six or 12 months, and 10 in whom standard testing eyed no mutations in the six-week sample. With a population detection limit of 0.1 percent, the PCR test routinely tracked down K103N or Y181C in samples judged mutation-free by standard sequencing (Table 1).

In Palmer's study the overall frequency of mutant virus, 69 percent, equaled the rate figured by Johnson.

If even these supersnooping assays see resistant virus in about two thirds of samples from women who take single-dose NVP, why do Richman and Clavel think virtually *everyone* who swallows the drug once ends up with resistant virus? Because Johnson's and Palmer's PCR tests espy mutations only in plasma samples, but most virus—resistant or otherwise—takes cover in deeper lairs.

Shayne Loubser (National Institutes for Communicable Diseases, Johannesburg) used real-time PCR to trawl for mutations locked up in viral DNA inside peripheral blood mononuclear cells (PBMCs) [abstract 102]. The good news is that he graphed rapidly dwindling K103N frequencies in DNA over time, seeing almost none after 12 months. The bad news is that few virologists in the audience sounded encouraged. One observed that more resistant virus probably lurks in other vaults—like memory cells in lymphoid tissue. Loubser agreed but maintained that his PBMC data confirm a marked overall dropoff with time. Retrovirus dean John Coffin (US National Cancer Institute, Frederick, Maryland) said other workers have had more success than Loubser in logging persistent mutations in PBMCs.

Trying nevirapine a second time

Arguments over persistence of NNRTI-resistant virus boil down to one burning question: What does this resistance mean clinically? The only published study to address this question, involving Thai women taking NVP for their own health, found equivalent six-month CD4 gains in women with and without earlier exposure to the drug.¹ But women who took one NVP dose earlier had a worse six-month virologic response than those starting the NNRTI for the first time, and women with genotypic evidence of resistance to NVP did even worse.

Another clinically crucial question is how well NVP will prevent HIV transmission when women try the single-dose regimen a second time. A case-control study by Neil Martinson (Johns Hopkins University, Baltimore) tried to find an answer, but his conclusion did not satisfy everyone [abstract 103].

This prospective study involved women taking NVP to avert transmission in a second pregnancy. The 75 "cases" had all tried single-dose NVP before, whereas the 132 controls had not. Martinson counted eight transmissions among cases (10.7 percent) versus five in controls (3.8 percent). In an analysis factoring in other transmission risks, those rates meant that women trying single-dose NVP a second time had a 2.3 times higher risk of giving their infant HIV. But because of the wide 95 percent confidence interval (CI) around that adjusted odds ratio (OR) (0.7 to 7.6), Martinson concluded that NVP works as well in a second try.

Not everyone agreed. Dissenters argued that the wide confidence interval may not mean repeat NVP works as well as first-time NVP, but that the study lacked statistical power to discern a clear difference.

Resistance during breast feeding

Another clinical concern arose in a study of infants taking NVP or lamivudine (3TC) monotherapy to ward off HIV in breast milk [abstract 93]. The resistance risk proved particularly high in 26 neonates studied by Marina Giuliano (Istituto Superiore di Sanità, Rome) because they all picked up HIV at birth or shortly afterwards, though the virus went undetected at the time. Retrospective study showed that 20 infants had HIV four days after birth, five by three weeks, and one by six weeks.

Samples collected about two weeks after 3TC prophylaxis began showed the 3TC-evoked M184V mutation in nine of 13 children, the NNRTI K103N mutation in one, and the zidovudine (AZT)-related M41L in another. All of the M184Vs

Table 1. NNRTI mutations after single-dose nevirapine

Number of women	Assay	Samples with K103N or Y181C (%)		
		6 weeks	6 months	12 months
8	Standard sequencing	100	100	0
	Allele-specific PCR	100	100	88
11	Standard sequencing	100	0	0
	Allele-specific PCR	100	80	45
10	Standard sequencing	0		
	Allele-specific PCR	50		

Source: Sarah Palmer, abstract 101.

disappeared a median of five months after prophylaxis stopped, but M41L and K103N hung on in plasma samples. Ten of 13 children taking NVP prophylaxis had one or more NNRTI mutations soon after treatment began. All of those mutations endured for months after treatment stopped.

Giuliano urged wider use of rapid HIV assays after birth to avoid exposing infected infants to prophylactic monotherapy.

READING RESISTANCE

At best, most resistance studies show that one mutation or another provoked by drug A but not drug B leads to faster virologic failure. Often, expert readings of resistance results suggest far less. So everyone should sit up straight when a particular resistance pattern foretells shorter survival, which is what happened in a study of 1,388 British Columbians who started potent therapy from August 1996 through July 2000 [abstract 712]. After a median 52.7 months of follow-up (interquartile range [IQR] 40.0 to 67.1 months), the Vancouver group found a higher risk of death with NNRTI mutations and an apparently *protective* effect with protease inhibitor (PI) mutations.

Robert Hogg (British Columbia Centre for Excellence in HIV/AIDS Vancouver) counted 238 deaths in the cohort for an all-cause mortality of 17.2 percent. Genotyping 3,120 viral samples—a median of one per person—he found resistance-linked mutations in 395 people (28.5 percent), including 271 isolates (68.1 percent) with resistance to 3TC, 138 (34.9 percent) with resistance to other nucleoside reverse transcriptase inhibitors (NRTIs), 199 (50.3 percent) with resistance to NNRTIs, and 106 (26.8 percent) with resistance to PIs. Nearly half of the resistant isolates—43.8 percent—had double-class resistance, and 7.9 percent had triple-class resistance.

A multivariate model of baseline and time-dependent factors rounded up some familiar suspects in shortened survival—older age, less physician experience with HIV, worse adherence, lower baseline CD4 count, and higher baseline viral load. Having resistant virus raised the risk of death 1.8 times in this model (95 percent CI 1.34 to 2.41). Another multivariate model retooled to weigh the mortal impact of specific mutation patterns found a heightened hazard ratio (HR) of death with NNRTI and non-3TC NRTI mutations, no clear pattern with 3TC-resistant virus, and apparent protection with PI-resistant virus:

- Non-3TC NRTI resistance: HR 2.93 (95 percent CI 1.44 to 5.96)
- NNRTI resistance: HR 2.07 (95 percent CI 1.19 to 3.60)
- 3TC resistance: HR 0.81 (95 percent CI 0.37 to 1.77)
- PI resistance: HR 0.32 (95 percent CI 0.11 to 0.97)

Hogg and resistance maven Richard Harrigan did not speculate on why failure of NNRTIs—but not PIs—ups the odds of death. But in a just-published study by this team, probably involving mostly the same people, Harrigan and Hogg found that first-line NNRTI therapy independently raised the risk of multiclass failure 1.84 times ($p = 0.001$).²

Resistance during drug holidays

As one structured treatment interruption (STI) stratagem after another falls on barren ground (see “Two more dead-end STI salvage studies” on page 74 of the March 2005 issue of the *IAPAC Monthly*), CD4-guided drug breaks remain a tempting (though possibly beguiling) option for people longing to shorten their time on treatment. A cross-border collaboration between clinicians in Orléans, France, and Madrid confirmed earlier reports that people with lower CD4 nadirs have to restart antiretrovirals faster during CD4-guided breaks [abstract 585]. But this tactic was not clinically innocuous—Kaposi’s sarcoma cropped up in one person during a drug break, and toxoplasmic retinitis in another.

To suspend treatment in this 94-person study, people needed a CD4 count above 450 cells/mm³ and a viral load under 50 copies/mL, and they had to restart if their T-cell tally fell under 350 cells/mm³ or if an opportunist arose. They could also resume treatment whenever they felt the urge. Thierry Prazuck (Regional Hospital Center, Orléans) reported that median months off treatment reflected lowest-ever CD4 counts:

- All study participants: 24.4 months off therapy
- CD4 nadir 200 to 350 cells/mm³: 17.5 months off therapy
- CD4 nadir 150 to 200 cells/mm³: 15.5 months off therapy
- CD4 nadir below 150 cells/mm³: 9.1 months off therapy

Even nine months of freedom from antiretrovirals probably sounds like a good deal to lots of people. But besides the risk of retinitis and other ugly setbacks, everyone should know that resistance also poses a threat during CD4-steered STIs.



That finding came from a randomized comparison of 87 people taking an STI and 30 continuing treatment [abstract 679]. Two lessons learned in earlier trials came home to roost in this one:

- STIs are a bad idea for people who once tried single- or double-NRTI therapy
- STIs are a bad idea for people taking an NNRTI

Looking for resistance mutations during and after drug breaks guided by CD4 counts or viral load, Lidia Ruiz (IrsiCaixa Foundation, Barcelona) found them in 32 of 87 break takers (37 percent). Among the 31 people with NRTI-linked mutations, 25 had sampled NRTI monotherapy or duotherapy before taking a stronger combo, and most of them had thymidine analog mutations (TAMs) reflecting this earlier treatment.

Nine of 19 people (42 percent) who suspended an NNRTI regimen ended up with nonnuke mutations. In seven of these nine the mutations arose during the drug break, and in two after they resumed treatment. Genotyping of pre-NNRTI viral DNA did *not* reveal these mutations. All told, new mutations sprang up in four people (5 percent) who had not taken one- or two-drug therapy in earlier days.

Together these studies tell a cautionary tale: Despite mostly gladsome news on CD4-guided drug breaks, these holidays can have unhappy endings. In a review talk at CROI, Diane Havlir (University of California, San Francisco)—no milquetoast when it comes to novel strategies—warned that CD4-guided breaks still need rigorous study to sort out their risks and benefits [abstract 181].

If common becomes rare, does rare become common?

When baseball hero and barroom sage Yogi Berra dismissed a familiar hangout with the epigram “no one goes there any more—it’s getting too popular,” he might have been describing today’s drug resistance patterns. Elbowing his way through a crowd of 128,456 viral isolates on tap at Virco, Alex Rinehart discovered that the “most common” mutation combinations are turning up less and less [abstract 684]. Rarities, conversely, abound.

Breaking isolates into six-month clusters based on 1998 to 2004 submission dates to Virco, mutation counters tallied more than 3,330 NNRTI mutation combinations not seen in earlier half-year periods, more than 17,200 NRTI mutation patterns making their debut, and more than 22,700 PI mutation arrays with no forebears in Virco’s vaults. At the same time, 97 percent of PI mutation sets, 95 percent of NRTI mutation sets, and 87 percent of NNRTI mutation sets showed up in 10 or fewer isolates.

Exercising understatement, Rinehart concluded that “previously

undetected combinations of mutations continued to be received at a steady rate.”

These findings should stir more than idle curiosity; they reflect the necessarily gnarled dynamics of viral evolution, as HIV beads strings of amino acid substitutions aimed to escape drug pressure and keep itself fit. While Virco’s Rinehart offered a satellite-high view of that breakneck evolution, Eoin Coakley (ViroLogic) snapped a submicroscopic close-up of a unique mutation tweak in one individual [abstract 716].

The man studied had a viral load of 6,547 copies/mL while taking NVP plus 3TC, abacavir (ABC), and tenofovir (TDF). Except for a quick taste of saquinavir (SQV) during a time when his viral load stayed under 50 copies/mL, he had tried no PIs. Keeping 3TC, ABC, and TDF, he traded NVP for atazanavir (ATV) and saw his viral load retreat to 118 copies/mL. Adding ritonavir (RTV) sent it below the 50-copy cutoff. But a few months later he endured a rebound to 7,535 copies/mL.

Genotyping after the rebound did not turn up I50L, the signature mutation seen with failure of unboosted ATV. But N88S, encountered *in vitro* but never apart from I50L in clinical isolates, did appear (along with some minor protease changes). Snooping through ViroLogic’s viral database, Coakley pulled up all I50L or N88S isolates without other primary PI mutations. Tracking the prevalence of N88S from the third quarter of 2003 to January 2005, Coakley charted a climb from 1.04 to 2.86 percent. Over the same period, I50L prevalence vaulted from 0.15 to 3.65 percent. Every N88S in the database proved susceptible to lopinavir (LPV) and amprenavir (APV), while more than 95 percent laughed off ATV and nelfinavir (NFV). The patient’s clinician swapped APV/RTV for LPV/RTV and his viral load sunk below 50 again.

This appears to be the first case of primary resistance to RTV-boosted ATV, Coakley noted. Whether N88S will routinely emerge as the culprit in such failures awaits further study. But this case study by ViroLogic neatly makes the point proposed in Virco’s mass analysis: Expect the unexpected.

But don’t expect top HIV clinicians to agree about genotypes, phenotypes, or both when picking rescue regimens. That conclusion emerged from a crafty exercise cooked up by Andrew Zolopa (Stanford University, California) with help from Stephen Becker (Pacific Horizon Medical Group, San Francisco), and some ViroLogic stalwarts [abstract 727]. They sweet-talked 109 clinicians attending regional advisory board meetings into picking new regimens based on actual genotypic (GT), phenotypic (PT), or GT-PT data—but with no clues from case histories.

Zolopa dealt out GTs, PTs, and GT-PTs in random order and made sure all samples had decreased susceptibility (PT resistance) to at least one drug. Otherwise the samples could have no, minimal, moderate, or significant PT-GT discordance, resensitization or hypersusceptibility to certain drugs, quantifiable differences in PT susceptibility without PT-GT discordance, or PT-GT discordance attributed to mixtures in genotype. This is not a test you want to take after sampling single malts. Zolopa and collaborators powwowed on consensus picks of “acceptable” or “unacceptable” antiretroviral options.

Given these ground rules, the percentage of “acceptable” calls may rank as a minor miracle. The median percentage of

regimens with at least three “acceptable” drugs was 65 percent (range 37 percent to 96 percent) for interpreting GTs, 86 percent (range 42 percent to 99 percent) for reading PTs, and 86 percent (47 percent to 97 percent) for PT plus GT. Demographics like professional degree, number of patients cared for, or self-assessed resistance acumen did not affect the results in a multivariate analysis.

Zolopa believes the results suggest that the resistance test used “may result in very different antiretroviral treatment regimens for some patients.” Using PT or PT plus GT may yield better results than GT alone, he proposed. But he cautioned that this study cannot clinch that conclusion because it did not factor in actual outcomes in the people whose virus got analyzed.

K65R, TAMs & company

The TDF-evoked K65R mutation and TAMs shun each other’s company. Even when they deign to share the same viral population, they almost never show up on the same genome, according to a detailed study by Urvi Parikh (University of Pittsburgh) [abstract 98]. She scoured the 2003 Lab Corp database to track down more than 56,000 isolates in which standard population sequencing spotted either K65R or TAMs. Then she subjected those samples to powerful single-genome sequencing to nose out recondite mutations.

K65R showed up in 1,881 samples (3.2 percent) and T215F/Y plus at least two other TAMs in 8,411 (14.2 percent). But only 24 samples—a piddling 0.4 percent—shared both K65R and T215F/Y plus two or more other TAMs. Some of those rare genomes also bore the infamous Q151M multi-NRTI resistance complex.

Parikh concluded that regimens including AZT and nucleosides or nucleotides that select K65R have a high genetic barrier to resistance and merit further study. Evidence of this high barrier came last year from Graeme Moyle (Chelsea and Westminster Hospital, London), who found that TDF plus Trizivir (AZT, 3TC, and ABC) shut down viral replication as well as Combivir (AZT/3TC) plus EFV after 48 weeks in previously antiretroviral-naive people.³ The pretreatment median viral load stood above 100,000 copies/mL in both treatment arms, and the median pretreatment CD4 count languished below 200 cells/mm³.

At the 12th CROI, two groups tested the triple nucleoside/tide regimen AZT/3TC/TDF without the extra oomph from ABC in treatment-naive people. French clinicians reported four virologic failures and five toxicity dropouts among 42 people who took the regimen for eight months [abstract 599]. As Parikh predicted, none of the failures came with K65R plus TAMs. These French study participants started AZT/3TC/TDF with a median 233 cells/mm³ and a median load of 4.88 logs (about 75,000 copies/mL).

A Ugandan trial of the same triple therapy in antiretroviral-naive people with much more advanced disease—medians of 100 cells/mm³ and 333,000 copies/mL—found a 54 percent sub-50-copy response rate at 24 weeks in a missing-data-equal-failure analysis [abstract 22]. (See “Another try with triple nukes” on page 77 of the March 2005 issue of the *IAPAC Monthly*.)

The K65R substitution may emerge more often than previously reported when 3TC/ABC/TDF fails, closer scrutiny of the ESS30009 trial suggested [abstract 720]. Clonal analysis spotted K65R in samples from four of four people in whom researchers

originally blamed regimen failure on M184V/I alone [abstract 720].

Glaxo’s Peter Gerondelis and colleagues believe these findings

“suggest that the incidence of K65R at week 12 was higher than the 54 percent originally reported.”

Emergence of K65R plus M184V is not the end of the world for previously treatment-naive people—only the possible end of full susceptibility to TDF and all NRTIs except AZT.⁴ Indeed, Roland Landman (Bichat-Claude Bernard Hospital, Paris) reported that virus pocked with K65R and M184V looked *hypersusceptible* to EFV, NVP, and AZT by phenotypic fingerprinting [abstract 710]. Most of 22 people who picked up K65R with or without M184V returned to the realm of undetectability after 14 to 177 weeks of rescue therapy.

Fourteen of these people got K65R and other mutations in the French trial of once-daily 3TC/ABC/TDF⁵ and eight in the Gilead comparison of TDF with stavudine (d4T) plus 3TC and EFV.⁶ Fourteen people had K65R with M184V, five had those mutations plus NNRTI-induced changes, and three had K65R with NNRTI mutations. Sixteen people started a PI (LPV/RTV in 10), and six still naive to NNRTIs started EFV or NVP. Thirteen people started AZT, 11 started didanosine (ddI), nine kept TDF, and five kept 3TC.

After a median 48 weeks of follow-up, 19 people (88 percent) chiseled their viral load to a sub-50 sum. Among the three people who did not, two earned a “lost-to-follow-up” label and one had adherence problems. Two people in whom 3TC/ABC/TDF had failed kept taking those drugs and merely added EFV; both got below 50 copies/mL. Phenotyping in the whole group suggested that K65R/M184V mutants remained fully susceptible to either AZT or d4T and partly susceptible to TDF.

Does TAM-tainted virus respond to emtricitabine (FTC) as well as to 3TC? Early results from 3TC’s maker, Glaxo, suggest these mutants may stay susceptible to 3TC more often than to FTC, though the differences in many cases were slim [abstract 713]. And as Glaxo’s Lisa Ross observed, the results for FTC need clinical verification because she inferred the phenotypic (“fold-change”) cutoff for FTC from 3TC data.

Ross figured median fold-change resistance to the two NRTIs in six mutant sets, defining TAMs as M41L, D67N, K70R, L210W, T215F/Y, and K219E/H/N/Q/R. Almost all K65R mutants readily shrugged off both 3TC and FTC, whereas virus with two or three TAMs at positions 67, 70, or 219 looked considerably more susceptible to 3TC (Table 2).

But if 3TC has an edge over FTC in slamming 67-70-219 TAMs, d4T may outpunch AZT on this so-called TAM-2 pathway, according to a 625-sample analysis by Alessandro Cozzi-Lepri (Royal Free and University College Medical School, London) [abstract 708]. The study also confirmed that TAM-1 and TAM-2 clustering does not happen by chance alone.

Cozzi-Lepri started with 625 EuroSIDA isolates trammelled by two or more TAMs. Two independent labs figured that 343





Table 2. Susceptibility of K65R and TAMs to FTC or 3TC

	FTC			3TC		
	n	MFC	Over FC cutoff (%)	n	MFC	Over FC cutoff (%)
K65R only	31	6.7	93.5	161	8.8	98.1
T69 insertions (± TAMs)	10	14.7	90.0	96	9.2	89.6
2 or 3 TAMs at 41, 210, 215 (TAM-1 pathway)	61	2.3	9.8	450	1.9	6.2
2 or 3 TAMs at 67, 70, 219 (TAM-2 pathway)	27	2.2	18.5	227	1.9	6.2
Any 3 or 4 TAMs	89	3.3	49.4	645	3.0	38.8
Any 5 or 6 TAMs	22	6.8	100	183	4.9	79.2

FC = fold change; MFC = median fold change in susceptibility.
Source: Lisa Ross, abstract 713.

samples (54.9 percent) took the TAM-1 path, 114 (18.2 percent) preferred the TAM-2 path, and 168 (26.9 percent) wandered along other ill-defined routes. One factor independently predicted evolution of the TAM-2 path and two factors lowered the chance of a TAM-2 trail at the following adjusted OR and 95 percent CIs:

- Longer exposure to AZT mono or dual therapy (per year): OR 1.25, 95% CI 1.14 to 1.36, $p = 0.0001$
- Presence of the V118I reverse transcriptase mutation: OR 0.34, 95% CI 0.20 to 0.60, $p = 0.0002$
- Higher viral load at time of resistance test (per log higher): OR 0.81, 95 percent CI 0.65 to 1.00, $p = 0.05$

Even more intriguing was the suggestion that d4T-containing regimens may beat back TAM-2 virus, while AZT regimens roll over when faced with those mutations. Among people with a TAM-2 profile, the six-month viral load drop averaged 1.27 logs with d4T but only 0.19 log with AZT ($p = 0.02$). Response rates to TAM-1 virus were equivalent with d4T (-0.71 log) and AZT (-1.17 log). But Cozzi-Lepri adjured all to interpret those changes with caution: Because this is a cohort study—not a trial randomizing people to d4T or AZT—irksome “residual confounders” may sway the results.

TOXIC KNOCKS

The biggest toxicity news from the 12th CROI involved the heart. D:A:D study collaborators confirmed a growing risk of myocardial infarction (MI) with longer time on antiretrovirals. But they also found that overall MI risk dwindled in D:A:D’s latest follow-up years. There may be good reasons for that dwindling, as prescribers switch from PIs to NNRTIs or to the lipid-friendly PI ATV. Fish oil, attendees learned, may grease the skids to lower triglycerides.

On the lipodystrophy front, a randomized study saw benefits for TDF over ABC when swapping out a thymidine analog. Although a cohort study logged signs of kidney problems with TDF, the clinical significance of those hints (if any) remains obscure. A person’s genetic make-up may sway the risk of that primeval NRTI problem, neuropathy.

A waning heart risk with HIV?

After more than six years of follow-up in the massy D:A:D cohort, every added year of combination antiretroviral therapy (ART) boosted the MI risk 1.17 times (95 percent CI 1.11 to 1.24, $p < 0.0001$) [abstract 42]. Compared with no treatment, each annual increment in multidrug therapy inched that risk ever upward at the following relative rates (RR):

- <One year: RR 1.83 ($p = 0.10$)
- ≥One <2 years: RR 1.94 ($p = 0.05$)
- ≥Two <3 years: RR 2.25 ($p = 0.01$)
- ≥Three <4 years: RR 3.09 ($p = 0.0002$)
- ≥Four <5 years: RR 3.24 ($p = 0.0001$)
- ≥Five <6 years: RR 3.20 ($p = 0.0003$)
- ≥Six years: RR 4.34 ($p = 0.0001$)

For those who have been cryohibernating for the past few years, D:A:D is an 11-cohort European, Australian, and US assemblage of 23,441 people with HIV infection. Wafaa El-Sadr (Harlem Hospital, New York) reported that 18 percent remain innocent of antiretrovirals, 82 percent have tried NRTIs, 69 percent PIs, and 35 percent NNRTIs. The cohort is heavy in smokers, with a prevalence of 47 percent, and 42 percent have lopsided lipids. At last count the D:A:D team tallied 277 MIs for an overall incidence of 3.6 per 1,000 person-years.

A multivariate analysis singled out six factors that independently predicted a higher MI risk:

- Each extra year of combination antiretrovirals
- Each extra five years of age
- Being male
- Having a personal history of cardiovascular disease
- Having a family history of cardiovascular disease
- Smoking

For the first time D:A:D also dug up a possible explanation for the higher heart attack risk with combination therapy, and it was no surprise—bad lipid readings. Every time total cholesterol ticked up 1 mmol/L, the MI risk rose 12 percent (95 percent CI 1.04 to 1.21). Every time triglycerides doubled, the MI risk climbed 12 percent (95 percent CI 1.04 to 1.21). And every time high density-lipoprotein (HDL) cholesterol edged up 1 mmol/L, the MI risk hopped 15 percent (95 percent CI 1.06 to 1.24).

But how you construe D:A:D’s data depends on how you dice the numbers over time, as Caroline Sabin (Royal Free Hospital, London) showed in a separate analysis [abstract 866]. She split the cohort into four groups classified by risk factors at the end of four years—2000, 2001, 2002, and 2003. An analysis that controlled for surging treatment experience over time and the

ups and downs of risks and retaliatory tactics suggested that “the risk of MI has *decreased* over time, possibly as a result of improved targeting of intervention to those at high risk” [italics added].

Sabin weighed five risk predictors—current smoking; hypertension; high total cholesterol (≥ 6.2 mmol/L) or total-to-HDL cholesterol ratio (≥ 6.5) or low HDL cholesterol (≤ 0.9 mmol/L); family history of cardiovascular disease; and age 45 or older in men and 55 or older in women. She defined high risk as having an earlier MI or stroke, having diabetes, or having two or more of the above risk factors.

The proportion of people with two or more heart disease harbingers rose from 34.3 percent in 2000, to 37.4 percent in 2001, 41.0 percent in 2002, and 41.5 percent in 2003, largely because people got older, got heart disease, or got diabetes (from 3.5 percent in 2000 to 5.4 percent in 2003). And the proportion of people who picked up a “high-risk” label over these four years bulged from 36.0 to 39.3, 43.1, and 43.7 percent.

But D:A:D doctors and cohort members did not sit on their hands as heart disease headlines blared. From 2000 to 2003 the percentage of people taking antilipid drugs climbed from 3.5 to 7.6 percent. The quotient of D:A:D nicotine addicts rose from 47.4 percent in 2000 to 51.9 percent in 2002, then slipped to 45.0 percent in 2003. Among men over 45 and women over 55, average total cholesterol and triglycerides dwindled marginally over the years, from 5.4 to 5.2 mmol/L and from 2.0 to 1.9 mmol/L.

Mixing these variables in one model, Sabin learned that the relative hazard (RH) of a heart attack dipped significantly after 2001:

- 2000 (reference year): RH 1
- 2001: RH 1.13 (95 percent CI 0.79 to 1.61), $p = 0.51$
- 2002: RH 0.67 (95 percent CI 0.45 to 1.00), $p = 0.05$
- 2003/2004: RH 0.62 (95 percent CI 0.41 to 0.93), $p = 0.02$

Notably, the D:A:D team does not essay the arduous labor of sorting out MI risk by individual antiretroviral class or drug. So the precise effect of a worldwide turn to NNRTIs and to ATV in the past several years—if any—remains unknown in this cohort. But in the northern California cohort of Daniel Klein (Kaiser Permanente, Oakland), fervid adoption of ATV and swelling prescription of lipid-lowerers may be paying off [abstract 869].

Klein ranks among the premier tollers of the MI tocsin with his early report that men with HIV landed in the hospital for heart disease much more often than men without an HIV diagnosis.⁷ But that early work failed to forge a significant link between PI therapy and heart problems. And to this day Klein cannot make that link, though his case-control comparison now embraces 5,162 HIV-infected men tracked for 25,251 person-years and 42,531 controls followed for 295,005 person-years. Although the HIV group still has significantly higher coronary heart disease and MI rates, coronary “event” rates stratified by duration of PI therapy and by calendar period do not climb in “a clear linear fashion” over time.

Two reasons for this statistical shambling may be an Olympian leap in ATV prescriptions—from none in the second quarter of 2003 to 27 percent of prescriptions in the fourth

quarter of 2004 ($p < 0.0001$)—and a nearly equal leap in antilipid prescriptions among PI takers—from 1 percent in the fourth quarter of 1997 to 22 percent in the fourth quarter of 2004 ($p < 0.0001$). Klein did not report changes in NNRTI prescribing, but d4T fell from favor with a 48 percent prescription rate in 2001 to 17 percent in 2004 ($p < 0.0001$).

Aquitaine cohort researchers gauged smoking rates and PI and antilipid drug use from 2000 to 2003 to estimate their effect on carotid artery intima media thickness (IMT), a sturdy predictor of heart disease [abstract 871]. At the study’s starting point, reported Rodolphe Thiébaud (University of Bordeaux, France), 127 of 233 cohort members (60 percent) took a PI regimen, 138 (59 percent) smoked, five (2 percent) took fibrates, and none statins.

During the first year of follow-up, eight more people started fibrates, eight tried statins, 42 switched from their PI, and 10 quit smoking. Triglycerides, total cholesterol, and ominous low-density lipoprotein (LDL) cholesterol stayed stable in that period, but median IMT fattened from 0.55 to 0.57 mm ($p < 0.0001$).

Over the next two years, 52 more people abandoned PIs, 30 more started antilipid drugs, and 14 more stopped smoking. At this point the 36-month prevalence of lipid-clipping therapy measured 17 percent, non-PI therapy 60 percent, and smoking 51 percent. In this two-year stanza total cholesterol and LDL cholesterol fell significantly ($p < 0.0001$ and $p = 0.05$), as did median IMT (from 0.57 to 0.53 mm, $p < 0.0001$).

Thiébaud traced a nearly significant link between the descending IMT slope and the no-smoking trend ($p = 0.06$), while changes in lipids and PI use did not correlate with IMT slope in this analysis. The statistical gravitas of snuffing cigarettes ebbed some with further adjustment for age, gender, body mass index, and total cholesterol ($p = 0.11$).

Lest anyone become too encouraged by these trends, Paige Williams (Harvard School of Public Health, Boston) and US AIDS Clinical Trials Group (ACTG) comrades reported an atherosclerotic cardiovascular disease incidence twice as high as D:A:D’s (7.2 events versus 3.6 events per 1,000 person-years) [abstract 867]. And over half of the ACTG enrollees who succumbed to heart disease had less than a 10 percent baseline risk on the Framingham scale. But the ACTG cohort was much smaller than the D:A:D pack (643 people) and follow-up shorter (median 4.8 years). Also, an ACTG subset of 433 people with longer follow-up had a higher heart risk at baseline.



Nothing fishy about atazanavir or fish oil

A gurgling datastream from company-sponsored ATV trials documents improved lipid profiles in people who switch from other PIs to ATV. But it's always nice to see independent confirmation of those trends in a biggish cohort—something provided at CROI by Esteban Martínez (Hospital Clinic, Barcelona) and colleagues in the Spanish ATV early-access program [abstract 850].

This analysis involved 256 people with risky lipid readings (triglycerides above 500 mg/dL, total cholesterol above 200 mg/dL, LDL cholesterol above 130 mg/dL) for at least the past three months. All switched, notably, to RTV-boosted ATV, and many also traded their NRTIs for ddI, 3TC, and/or TDF. Triglycerides, total cholesterol, and non-HDL cholesterol all dropped significantly after six months (-21 percent, $n = 141$; -13 percent, $n = 143$; -14 percent, $n = 108$) and 12 months (-43 percent, $n = 32$; -22 percent, $n = 32$; -24 percent, $n = 28$). The total-to-HDL cholesterol ratio ebbed from 5.7 at baseline to 4.9 at month 12 ($p = 0.006$).

Meanwhile, the switch to ATV and other regimen rejiggers boosted the proportion of people with a viral load under 500 copies/mL from 50 percent to 74 percent at month six ($n = 141$) and to 75 percent at one year ($n = 32$). CD4 readings rose by 45 cells/mm³ at month six and 48 cells/mm³ at month 12. Three people had to quit ATV because of jaundice and one because of spurting transaminases. All told, eight people stopped ATV because of side effects.

At the 11th CROI in 2004, a 16-week trial failed to find a triglyceride advantage for fish oil (omega-3 fatty acid) plus diet and exercise counseling versus counseling alone.⁸ That small study used a European product called Coromega at a dose of about 3 g daily. At the 2005 conference a much bigger double-blind, placebo-controlled comparison of another fish oil physis, Maxepa, significantly purged high triglycerides after eight weeks, and that drop held up through week 16 [abstract 39].

Pierre De Truchis (Raymond Poincaré Hospital, Garches, France) and coworkers recruited 146 people with triglycerides above 3 g/L while taking a stable antiretroviral combo. When dietary advice for four weeks failed to cut triglycerides to 2 g/L in 122 people, the researchers randomized them to take 2 g of Maxepa three times daily or placebo for eight weeks. Over the next eight weeks, everyone took Maxepa.

At week eight mean triglycerides plunged from 4.4 to 3.4 g/L with Maxepa while inching from 4.7 to 4.8 g/L with placebo ($p = 0.0033$). At that point 22.4 percent taking fish oil and 6.5 percent taking placebo notched a normal triglyceride level ($p = 0.126$). During the study's eight-week open-label phase, triglycerides stayed flat in the Maxepa group and sank to 3.4 g/L when the placebo group switched to fish tabs.

Side effect rates did not differ between groups during the eight-week blinded phase. Maxepa had no impact on viral load or CD4 count in this study. The fish tabs has no known interactions with

antiretrovirals, although De Truchis did not measure drug levels. Maxepa's thrice-daily dosing may seem rigorous to people getting used to once-a-day antiretrovirals.

Tenofovir versus abacavir as switch option

When several studies showed that trading d4T or AZT for ABC reversed limb fat losses, ABC became the natural choice in such swaps. But with TDF available, is ABC the best choice? To find out, Graeme Moyle (Chelsea and Westminster Hospital, London) randomized 105 people with moderately severe lipoatrophy to replace d4T or AZT with TDF or ABC [abstract 44]. Limb fat gains were equivalent in the two groups after 48 weeks, but TDF appeared to beat ABC in a metabolic marker contest.

Everyone in this largely white, male study group had a viral load below 50 copies/mL for at least 24 weeks on the same regimen. For most people (63 percent assigned to TDF and 74 percent assigned to ABC), that regimen did not include a PI. The groups differed little in median age, nadir CD4 count, current CD4 count, or total limb fat (3.0 kg in the TDF arm and 2.9 kg in the ABC arm). The TDF group had a longer antiretroviral history (median 5.7 versus 4.9 years).

Three of 52 people (6 percent) randomized to TDF quit the study before week 48, compared with eight of 53 (15 percent) assigned to ABC. One person stopped TDF because of toxicity, and three dropped ABC for that reason—all with a hypersensitivity reaction. A missing-data-equal-failure analysis of the 2005 conference (DEXA) arm-plus-leg fat at week 48 figured a 393-g gain with TDF and a 316-g rally with ABC, a nonsignificant difference ($p = 0.97$).

Subanalyses of 48-week DEXA results suggested that people switching from AZT did better with ABC (+210 g versus +66 g with TDF), while people taking d4T at baseline gained more with TDF (+529 g versus +375 g with ABC). Study participants taking a non-PI regimen also did somewhat better with TDF (+432 g versus +247 g). There weren't enough people in these subgroups to make these differences significant. But Moyle told *IAPAC Monthly* that the fat recovery in the group stopping AZT—combined with data from ACTG 384 and ACTG 5125s [abstract 40]—suggest that “AZT is a player in lipoatrophy and should be avoided in the long term.”

People assigned to TDF did enjoy significantly greater (though small) improvements in certain lipids:

- Total cholesterol: -0.2 mmol/L with TDF versus no change with ABC ($p = 0.016$)
- LDL cholesterol: -0.1 mmol/L with TDF versus no change with ABC ($p = 0.043$)
- Triglycerides: -0.17 mmol/L with TDF versus no change with ABC ($p = 0.031$)

In follow-up questions Andrew Carr (St. Vincent's Hospital, Sydney) noted that more people assigned to TDF took d4T at baseline (77 percent versus 59 percent assigned to ABC). Adjusting the lipid analysis for that variable, he proposed, may make the significance of these differences disappear. Either way, TDF may be the safer short-term switch option, given the low but real risk of hypersensitivity with ABC.

A 24-week study at 15 ACTG sites found better peripheral fat gains with a non-NRTI regimen than with a simple switch of d4T or AZT to ABC [abstract 45LB]. Robert Murphy (Northwestern University, Chicago) and colleagues randomized 27 people with lipoatrophy to continue their current regimen for 24 weeks, 37 to trade d4T or AZT for ABC, and 40 to eschew NRTIs entirely and start LPV/RTV plus NVP.

After six months the LPV/RTV/NVP group gained CT-measured subcutaneous thigh fat (the study's primary endpoint) while the other groups continued shedding thigh fat (+8.4 percent versus -0.2 percent with ABC and -0.32 percent in the control arm, $p = 0.06$). The non-NRTI group added 8.0 CD4 cells/mm³, while the ABC group lost 4.8 cells/mm³ ($p = 0.03$) and the control group picked up an extra 2.4 cells/mm³. Both the non-NRTI contingent and the ABC troop gained subcutaneous adipose tissue (+16.6 percent and +9.2 percent), while the control group lost 8.8 percent. And both the non-NRTI and ABC assignees lost much more visceral adipose tissue (-15.0 percent and -15.3 percent) than the control arm.

Murphy did not report changes in lipids or other metabolic markers. A second ACTG study found that switching to another no-nuke regimen—EFV plus LPV/RTV (533/133 mg twice daily)—restored limb fat but boosted total cholesterol, LDL cholesterol, and triglycerides [abstract 40].

Tenofovir, didanosine, bones, glucose, and kidneys

Just after CROI the makers of TDF and ddI warned European clinicians not to prescribe these drugs together—for anyone⁹—largely because regimens combining TDF and ddI with an NNRTI in treatment-naïve people with high viral loads looked surprisingly feeble.¹⁰⁻¹² A CROI report from the Swiss HIV Cohort Study addressed earlier findings of CD4 slippage with 300/400 mg of TDF/ddI daily [abstract 588]. Urs Karrer (Zurich University Hospital) found equivalent CD4 changes with TDF regimens lacking ddI and with TDF plus a weight-adjusted ddI dose below 4.1 mg/kg. A ddI dose above 4.1 mg/kg independently predicted a poor CD4 response in the Swiss cohort.

Other studies tracked bone, glucose, and kidney complications in people taking TDF with or without ddI. Worries over bone loss with TDF began when monkeys given high doses showed defects in bone building.¹³ Then a 144-week comparison of TDF with d4T (plus 3TC and EFV) charted lower spine density in the TDF group, though most bone mineral loss happened during weeks 24 to 48.⁶ Pursuing these leads, Nutrition for Healthy Living Cohort researchers measured total bone mineral density with DEXA scans over a median 2.9 years (IQR 1.5 to 4.1 years) in 283 men and 94 women [abstract 825]. The cohort included 100 people who took ddI at least part of the time during follow-up, 66 who took TDF, and 191 who took d4T.

Denise Jacobson (Tufts University, Boston) reported a median baseline CD4 count of 364 cells/mm³ and a median viral load below 1,000 copies/mL. The median change in bone density measured -0.17 percent yearly (IQR -0.8 to +0.43 percent, $p = 0.0004$). The loss came to 0.51 percent through three years of follow-up (IQR -2.5 to +1.3 percent).

In an analysis adjusted for age, gender, race, albumin, menopause, smoking, viral load and weight change, and time between visits, treatment with TDF ($p = 0.0002$), longer use of ddI

($p = 0.001$), and bilirubin above 2 mg/dL ($p = 0.0003$) independently predicted greater bone mineral loss. Longer treatment with d4T translated into less loss of bone density ($p = 0.003$).

Combining TDF with 400 mg of ddI daily raised the risk of hyperglycemia in a retrospective comparison of 78 people taking both drugs, 42 taking only TDF, and 57 taking only ddI [abstract 829]. Follow-up in this single-center study began before the recommendation to trim ddI doses with TDF, so the initial ddI dose was 400 mg in people weighing over 60 kg and 250 mg in those weighing less. During follow-up Theresa García-Benayas (Carlos III Hospital, Madrid) and coworkers cut the ddI dose to 250 mg for heavier people and to 200 mg for lightweights.

Fasting glucose averaged about 95 mg/dL in all study groups when follow-up began. After 12 months glucose rose to about 107 mg/dL in the ddI/TDF group while staying stable in the other groups ($p < 0.05$). Multiple linear regression analysis considering ddI use, TDF use, PI use, weight, age, and viral load found that lower weight ($p = 0.033$) and ddI/TDF ($p = 0.047$) independently upped the risk of hyperglycemia. Eighteen of 22 people whose glucose soared, and six of seven diagnosed with diabetes, had taken 400 mg of ddI with TDF

No one, one hopes, gives 400 mg of ddI with TDF anymore. Fewer physicians probably combine these drugs at all. But long-term kidney and bone risks with TDF remain to be fully defined. Joel Gallant (Johns Hopkins University, Baltimore) offered a step toward that goal by comparing creatinine levels and clearance in 344 people starting TDF and 314 starting another NRTI [abstract 820]. Both groups were about three quarters male and three quarters African American, and about one third got HIV from injecting drugs. The groups also balanced well in viral load and CD4 count and diabetes rates (12 percent with TDF and 8 percent in controls). Gallant published his findings just after the conference.¹⁴

Median baseline creatinine levels measured 0.8 mg/dL in both groups and median creatinine clearance 117 mL/min in the TDF group and 118 mL/min in controls. After a median 303 days of TDF therapy and 336 days of other-NRTI therapy, median creatinine levels climbed 0.15 mg/dL with TDF and 0.10 mg/dL in the control group ($p = 0.01$). Creatinine clearance dipped 13.3 mL/min with TDF and 7.5 mL/min in controls ($p = 0.005$). The drop in clearance measured 10 percent with TDF and 6 percent with non-TDF nukes ($p = 0.007$).

Gallant found two independent predictors of percent change in creatinine clearance—TDF use ($p = 0.006$) and CD4 count below 50 cells/mm³ ($p < 0.001$). These correlations held true when baseline clearance exceeded 50 mL/min—the signal to use full-dose TDF. Multivariate juggling also caught modest correlations between percent change in creatinine clearance and (1) baseline clearance below 50 mL/min and (2) diabetes ($p = 0.10$ for both). Age, gender, race, hypertension, hepatitis virus coinfection, and use of LPV/RTV or other specific PIs or NNRTIs did not correlate with a change in creatinine clearance.



“Although statistically significant,” Gallant noted, “the clinical significance of these findings is unclear,” partly because the drop in creatinine clearance did not force withdrawal of TDF. While 5.5 percent quit TDF at the time of maximal decline in renal function, 6.7 percent quit other NRTIs at that point.

Gallant reminded colleagues to test renal function before starting TDF and to follow advice on adjusting the dosing interval if clearance lies below 50 mL/min (see note 15).

Key to higher neuropathy risk?

What makes some people prone to peripheral neuropathy—especially if they take d-nucleosides—while others can take ddI/d4T for years without the slightest tingle? Because peripheral neuropathy may be a mitochondrial toxicity, Todd Hulgán (Vanderbilt University, Nashville) decided to parse mitochondrial haplogroups in people from ACTG 384, the trial that randomized treatment neophytes to ddI/d4T or AZT/3TC (plus EFV, NFV, or both) [abstract 43].

Hulgán compared 147 people who had grade 1 or worse neuropathy with 362 no-neuropathy controls. Predictably, most people who suffered neuropathy, 73 percent, took ddI/d4T. The median age measured 39 years in cases and 35 years in controls. The analysis involved only non-Hispanic whites, in whom mitochondrial haplogroup H predominates. People who fell into haplogroup T had a 2.8 times higher risk of neuropathy in a univariate analysis ($p = 0.019$) and a 5.5 times higher risk if they took ddI/d4T ($p = 0.006$). Multivariate sifting gleaned three independent neuropathy predictors:

- Older age (per year): odds ratio 1.05
- Randomized to ddI/d4T: odds ratio 2.57
- Mitochondrial haplogroup T: odds ratio 2.89

Hulgán stressed that these incriminating results must be confirmed in other cohorts. He did not determine mitochondrial DNA content or lactate levels in cases and controls.

GRIDLOCK

One hesitates to add a single phoneme to the farrago surrounding the New York City man who became infected with multidrug-resistant, dual-tropic virus and crashed from party-prowling vigor to AIDS in as few as four months. Not since the days of the “Berlin patient” has the HIV world put a single person under such a big microscope, as the media cheered on.

Readers with keen interest in this case surely memorized the details long ago, and this review will not add to the nimiety. At the 12th CROI, Martin Markowitz (Aaron Diamond AIDS Research Center, New York) offered a richly detailed poster printed in agate type, and those sundries appeared a few weeks later in a free-access *Lancet* article.¹⁶ Nor will this article broach the battle royal over the propriety of announcing the case at a press conference (except to imagine the ugly fracas if the case leaked before formal disclosure).

The salient facts brought forward by this sad history are not controversial at all:

- Some gay men—some of them in the later reaches of middle age—routinely and knowingly risk HIV infection, often while taking highly addictive crystal methamphetamine.
- Multidrug-resistant virus is circulating in gay communities.
- The viral strain that infected the New York case can use either X4 or R5 coreceptors, a nimble feature that may boost the risk of rapid progression.
- The progression rate in the New York case puts this man in the top 0.5 percentile of progressors in the Multicenter AIDS Cohorts Study, a cluster of gay men.
- Besides dual tropism, no viral or host factors yet considered explain the fast progression.
- Despite the multidrug resistance of this virus, it grows better than many nonmutant strains in lab dishes (see note 17).
- Possible susceptibility of the virus to only the fusion inhibitor enfuvirtide (ENF) and the NNRTI EFV compromises prospects for long-term control.

Across North America and Europe, the HIV epidemic has become a babel of viral subtypes, ethnic helter, and social skelter—applied in a rich schmeer of risk behaviors. Whoever suggested the original acronym GRID—for gay-related immune deficiency—must be happy that tag didn’t stick. Yet, although blacks in the United States and women worldwide shoulder disproportionate burdens of this plague, some of the most pungent recent trends involve the primal “risk group”—gay men in rich countries.

Fraternité à grands frais

Despite a big population of HIV-infected people from sub-Saharan Africa, France may be looking at a resurgent gay epidemic. Using a recent-infection assay for the first time on a national level, Caroline Semaille (Institut de Veille Sanitaire, Saint-Maurice) learned that gay sex accounted for 51.2 percent of new infections from March 2003 to March 2004, followed distantly by heterosexual intercourse (25.7 percent), injecting drugs (16.4 percent), and “others/unknown” (29.3 percent, a high quotient hinting at undisclosed same-sexism or drug use) ($p < 0.0001$).

These findings may mean that HIV has started spreading faster among French gays, Semaille concluded, that more gays got tested recently, or both. More testing, one could speculate, may reflect more trips to the sexually transmitted disease (STD) clinic for syphilis and lymphogranuloma venereum (LGV), the frightening emerging STD considered below.

Gay men in France are giving each other not only HIV, but also hard-to-treat genotype 4 hepatitis C virus (HCV), reported Marie-Laure Chaix (René Descartes University, Paris) [abstract 122]. In a cluster of 12 Parisians infected with the same HCV strain, two declined anti-HCV therapy. Nine of the remaining 10 did not respond to antiviral therapy in six months, and the tenth responded then relapsed.

Who's transmitting resistant virus?

Anybody may and many do, according to the most recent six-state analysis by the CDC [abstract 674]. In the contest to give bed or needle partners drug-resistant HIV, Diane Bennett reported, neither gays nor straights, whites nor blacks, women nor men, youngsters nor oldsters have pulled into a clear lead. Everyone got into the act in this 89-site review.

As Bennett noted, though, the analysis may under-represent people diagnosed in private practice or nonpublic centers. So it may under-represent people with better access to antiretrovirals. But men who have sex with men (MSM) made up the largest part of the cohort by exposure group (61 percent versus 25 percent heterosexual and 14 percent injecting drug users). Because the six states are Colorado, Illinois, Maryland, Michigan, Virginia, and Washington, the survey missed the biggest gay urban centers.

Bennett and collaborators collected 787 samples from newly diagnosed (not necessarily recently infected), untreated people and genotyped them for reverse transcriptase and major protease mutations. The overall rate of resistant virus transmitted in 2003-2004 measured 14.5 percent, with NNRTI-resistant virus at the head of the class (8.4 percent). The survey found 24 people (3.1 percent) with virus resistant to two or more antiretroviral groups. So, although transmission of multidrug-resistant virus remains rare in the United States, it is hardly a freak phenomenon.

A substudy of 633 demographically grouped people revealed no differences in rates of infection with resistant virus by race or ethnicity, HIV transmission group, age, or gender (Table 3).

The overall transmission rate in the CDC survey—14.5 percent—was lower than the 19.7 percent found in a North Carolina study and much lower than the 24.1 percent figured in a largely gay New York City population by Anita Shet (Aaron Diamond AIDS Research Center) [abstract 289]. And the rate in New York, Shet reported, is on the rise. Her study involved 112 people with acute or recent infection who came to the Aaron Diamond Center in 2003 and 2004. All but two were men, most of them gay. The group's age averaged 34.3 years and ranged from 19 to 56 years.

Twenty-seven people (24.1 percent) had virus bearing at least one resistance mutation, and 11 (9.8 percent) had mutations conferring resistance to more than one antiretroviral class—trebling the rate in the CDC six-state study. Multiclass resistance rose significantly in this cohort since 2000 ($p = 0.03$). Three people (3.1 percent) had virus with mutations to the first three antiretroviral classes. If there is any good news here, it is that no one had mutations to the fusion inhibitor ENF and that people infected with resistant virus responded to treatment as well as those with wild-type virus.

As in the six-state CDC audit, transmission of NNRTI-resistant virus is climbing in New York City. Shet recorded NNRTI mutations in 7.1 percent in 2003-2004 versus 2.6 percent in 1995-1998 ($p = 0.09$). This trend toward swelling transmission of NNRTI mutations may reflect the relatively greater fitness of this virus compared with PI or NRTI mutants—or even wild-type virus (see note 17).

The bustling trade in NNRTI mutant virus between sex partners “necessitates caution when considering initial empiric combination therapy with NNRTIs,” the Aaron Diamond team counseled. They now start treatment of acute infection with a boosted PI regimen until they get genotyping results.

Table 3. Prevalence of transmitted drug-resistant virus*

	Variable	Percent
Race or ethnicity	Black (n = 301)	14.2
	Hispanic (n = 99)	13.6
	White (n = 213)	15.3
	Asian/Pacific islander (n = 15)	15.4
Transmission group	Gay/MSM (n = 387)	15.9
	Heterosexual (n = 157)	13.0
	Injecting drug user (n = 89)	14.1
Age group	<25 years old (n = 95)	11.3
	25-44 years old (n = 411)	14.6
	45-64 years old (n = 119)	13.2
Gender	Men (n = 517)	14.9
	Women (n = 116)	13.8

*The analysis involved 633 people in six US states.

Source: Diane Bennett, abstract 674.

Charles Hicks (Duke University, Durham, North Carolina) looked for resistance mutations in two North Carolina groups of acutely or recently infected untreated people—110 referred to HIV clinics at Duke or the University of North Carolina (the “clinic” group) and 127 diagnosed at state-run HIV testing centers (the “state” group) [abstract 673].

The clinic and state groups did not differ much in age, with medians of 27 years (range 17 to 89 years) in the clinic and 30 years (range 15 to 59) in the state. More people in the clinic population were men (90 percent versus 68 percent) and gay (65 percent versus 39 percent), while the state program had a higher proportion of blacks (61 percent versus 43 percent).

The groups did not differ much, however, in rates of resistant virus. Overall, 25 (19.7 percent) had virus with at least one resistance mutation, and four (3.1 percent) had mutations rendering virus resistant to more than one class. Unlike the CDC and Aaron Diamond populations, the North Carolina groups had higher rates of resistance to NRTIs (7.1 percent) than to NNRTIs (6.3 percent). PI resistance prevalence measured 3.1 percent. Hicks told *IAPAC Monthly* that he could verify no risk difference by HIV transmission category. The largest proportion of those infected with resistant virus—but not a majority—got infected through gay sex.



Together these two studies suggest a sadly similar rate of resistance transmission in rural and urban North Carolina and on New York's mean streets.

Hector, Jonah, Leon, and Cody

Soon after people first get infected with HIV, they may be particularly prone to adding a second or "super" infection, proposed Robert Grant (Gladstone Institute, San Francisco) [abstract 287]. Decoding virus from 104 recently infected people with samples from two or more time points, he found viruses with highly divergent sequences in seven people. Independent analysis of virus from four of these seven at additional time points confirmed that they picked up first one HIV, then another. Further study of the other three is under way.

Code naming these four men Hector, Jonah, Leon, and Cody, Grant reported some particulars of their superinfections:

- Hector: A highly divergent virus appeared 16 to 44 weeks after his first infection.
- Jonah: A superinfecting strain showed up when he began treatment for gonorrhea.
- Leon: A second virus appeared just before rapid progression to AIDS.
- Cody: A wild-type virus replaced multidrug-resistant HIV 43 to 53 weeks after his first infection.

Why does superinfection seem more likely in recent seroconverters? Grant suggested that this trend "may reflect a window period for susceptibility (as in nonhuman primate research), or seroconverters may harbor several viruses that appear sequentially due to viral escape for immunologic reasons." Superinfection may become rarer during chronic HIV infection because of (1) specific antiviral immune responses to partner viruses, (2) viral interference, or (3) nonspecific immune responses.

Whatever the mechanisms, superinfection is on the upswing in the San Francisco Bay Area. These four (and possibly seven) cases arose in the last 195 person-years of observation. Grant saw none in the preceding 56 person-years.

Acute HIV's irreversible rampage

If a few insights into the threats of superinfection or infection with resistant virus cannot inspire a sober regard for HIV's wrath, watching the Webcast of a CROI plenary talk by Daniel Douek (US National Institutes of Health, Bethesda) might do the trick [abstract 127, see note 18].

People who blithely risk HIV infection (and maybe even some clinicians who see them) may consider acute infection a nasty but self-limiting sweaty bout that does little immediate damage—surely nothing that antiretrovirals can't fix five or six years down the road. Wrong. Reviewing his own recent work and that of others, Douek took the body count of HIV's early blitzkrieg:

- The primary target of acute HIV infection is the body's total battalion of memory CD4 cells—the very cells the body needs to counter other invaders.
- As many as 60 percent of memory CD4s can be infected in this acute assault.¹⁹

- The memory CD4 infection rate is more than 100 times higher in acute infection than in chronic infection.
- After 14 days of infection, 80 percent of infected memory CD4s are dead—half of all memory CD4 T cells.
- HIV rapidly and directly stifles proliferation of thymus cells—potential replacements for obliterated memory T cells.²⁰

All of this happens *before* seroconversion, while many just-infected people sit home from work, wondering how they got "the flu." The wasted CD4 troops never bounce back—and this onslaught is visually awesome, as Douek demonstrated by contrasting a slide of normal intestinal lymphoid tissue and the blasted mucosa inside a recently infected person. Before an HIV antibody test even signals infection, virus-induced inflammation burns through the bowels, replacing healthy mucosal tissue with collagen. For those without medical training, collagen is the stuff that makes up crusty cartilage and bone—not at all what you want in your guts.

"This doesn't look like a viral infection," Douek opined. "This looks like chemotherapy."

A new—and painful—STD

HIV came from tropical climes. And until the past year or two, the tropics were the only place one saw more than the odd case of LGV, the hard-to-diagnose, writhesome chlamydial infection that can rock the rectum and boost the risk of HIV transmission. That changed last November when Dutch health authorities cited 92 cases over the preceding 17 months—rather than the usual one or two—most of them in gay or bisexual men.²¹ At CROI, epidemiologists from France detailed an explosive outbreak there [abstract 895].

Magid Herida (Institut de Veille Sanitaire, Saint-Maurice, France) and colleagues retrospectively analyzed stored rectal specimens from January 2002 to April 2004 and prospectively rated samples from five Paris STD clinics and the national reference center in Bordeaux. They counted three LGV cases in 2002, 18 in 2003 (13 in the last quarter), and 102 in the first 11 months of 2004.

Collecting epidemiologic data from the first 14 people with rectal LGV, Herida found that all were gay men reporting unprotected anal sex with pick-up partners. None had visited an LGV-endemic area. Eight (57 percent) had HIV infection, nine (64 percent) had another STD in the last year, and all had anorectal signs or symptoms.

Symptom duration ranged from 11 to 120 days before diagnosis (median 50 days) and included rectal pain, discharge, and tenesmus (painful spasm of the urogenital diaphragm). Constipation, inguinal ulceration, and inguinal lymphadenopathy also characterize this disease. Three people with HIV had fever, and eight had "deep, extended rectal ulcerations." One man with a late diagnosis endured "a rectal tumor-like stricture." LGV is tough to diagnose, the French team observed, because it may mimic rectal carcinoma or Crohn's disease. Three HIV-infected people had cancer-like lesions.

From the Netherlands, Joke Spaargaren (Municipal Health Service of Amsterdam) and coworkers reported a new *Chlamydia trachomatis* strain causing LGV in gay men [abstract 896]. Because the earlier Dutch LGV outbreak involved gays in Rotterdam, he wondered if the STD made an earlier debut in Amsterdam. To find out, Spaargaren analyzed 82 rectal samples from 72 men who came to the health service

STD clinic with proctitis in 2002 and 2003. Proctoscopic exam separated them into two groups—42 symptomatic men with pussy anal seepage or bloody ulcerative rectal growths, and 32 without symptoms or rectal mucosal inflammation.

With polymerase chain reaction (PCR)-based genotyping and gene sequencing, Spaargaren learned that 39 of 51 samples from symptomatic men (78 percent) bore a new L2b strain of *C. trachomatis*, as did 13 of 31 samples (42 percent) from asymptomatic men. Most of the men with LGV were gay. Spaargaren concluded that the Dutch LGV outbreak can be traced back at least as far as 2002 in Amsterdam.

Staph too tough for methicillin

Methicillin-resistant *Staphylococcus aureus* (MRSA) infection crops up in children, prisoners, athletic teams, and now HIV-infected gay men. In many HIV clinics, MRSA causes more community-acquired staph infections than methicillin-sensitive *S. aureus* (MSSA). That's certainly true in the Harbor-UCLA Medical Center, reported Gunter Rieg [abstract 877]. And MRSA rates are rocketing down the road at the Owen Clinic of the University of California, San Diego, according to Christopher Mathews [abstract 142].

In a retrospective cohort analysis of 3,455 HIV-infected people who visited the Owen Clinic at least once between January 2000 and December 2003, Mathews cataloged 94 cases of MRSA, 38 (40 percent) defined as community acquired and 56 (60 percent) as nosocomial (probably picked up in a hospital or extended-care facility, or from an indwelling catheter). He linked only one factor to nosocomial acquisition of MRSA: cotrimoxazole resistance raised the risk 12.4 times.

Diagnosis of community-acquired or nosocomial MRSA jumped more than six times over the four years of study, from under one case per 100 person-years before 2003 to about five per 100 person-years in the second half of 2003. In a multivariate analysis, heterosexual transmission of HIV lowered the risk of MRSA 90 percent (adjusted HR 0.1, 95 percent CI 0.0 to 0.7, $p = 0.012$). Mathews told *IAPAC Monthly* that 65 percent of those with MRSA were gay men who did not inject drugs and 12 percent were gays who did shoot up. Taking antiretrovirals in the past half year trimmed the MRSA risk 40 percent ($p = 0.02$), while a low CD4 count or a high viral load independently raised the risk:

- CD4 <50 cells/mm³: HR 2.5, 95 percent CI 1.4 to 4.7, $p = 0.003$
 - RNA 3 to 3.99 logs (versus <3 logs): HR 2.1, 95 percent CI 1.0 to 4.4, $p = 0.059$
 - RNA 4 to 4.99 logs (versus <3 logs): HR 3.2, 95 percent CI 1.7 to 6.0, $p < 0.0001$
 - RNA ≥5 logs (versus <3 logs): HR 4.2, 95 percent CI 2.1 to 8.2, $p < 0.0001$

Mathews cautioned that the climbing incidence may reflect heightened scrutiny as clinicians learn about MRSA, and unmeasured confounders like active substance abuse

or short-term antibiotics could fudge the findings. Even so, the close correlation between poor control of HIV and MRSA “suggests a potential direct effect of HIV on antistaphylococcal defenses.”

How MRSA travels from one person with HIV to another remains unknown. Rieg and UCLA colleagues explored a nasal route, hypothesizing that gay men with HIV carry MRSA more often than MSSA in nasal secretions. They culled suspect secretions from 194 gay men attending their clinic and found *S. aureus* in 51 samples (26.3 percent). But 43 staph-laden samples (22.2 percent) carried MSSA compared with eight (4.1 percent) that bore MRSA.

Rieg rated seven of the eight MRSAs as community acquired, because one carrier had been in the hospital in the past half year. MRSA proved more common among African Americans (five of eight cases) and among people with a college education (seven of eight). Comparing the eight people with MRSA and the 186 without it, he tied three factors to the resistant bug:

- Skin infection in past six months (63 percent versus 19 percent, $p = 0.02$)
- Close contact with someone with a skin infection in the past six months (50 percent versus 6 percent, $p = 0.01$)
- Older age (mean 46.8 versus 40.6 years, $p = 0.06$)

Because few HIV-infected gays in this population carry MRSA in the nose, Rieg suggested that skin-skin or skin-fomite contact may explain transmission. (A fomite is any object that may carry a pathogen.) An alternate explanation may be that nasal MSSA picks up the *Mcc/4* gene conferring methicillin resistance before inciting active infection.

Will anyone be scared?

The temptation to drape oneself in censorious dudgeon over the self-destructive sexploits of today's party gays is probably best stifled. One could just as readily wax wrathful over down-low black guys whose crypto-flirtations expose their girlfriends to HIV, or over straight African dandies who prey on adolescents.

But it's hard to answer Harold Jaffe's (University of Oxford, England) question about why gay men still risk their health almost 25 years after he helped us understand how HIV spreads. Speaking at CROI about public health worries stirred by the New York City case, Jaffe defused the fluster over using case reports to scare people into better behavior.

“The important thing is to put out the facts,” he said. “If the facts are scary, then people will be scared.”²²

But given what we already know of the rampant nihilism among many sexually active gays, one wonders what it takes to scare them. ■

Mark Mascolini writes about HIV infection (markmascolini@earthlink.net).

References and Notes

1. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med* 2004;351:229-240.
2. Harrigan PR, Hogg RS, Dong WW, et al. Predictors of HIV drug-resistance mutations in a large antiretroviral-naive cohort initiating triple antiretroviral therapy. *J Infect Dis* 2005;191:339-347.
3. Moyle G, Nelson M, Higgs C, et al. A randomised open label comparative study of Combivir + efavirenz (2 class triple therapy) versus Trizivir + tenofovir (single class quadruple therapy) in initial therapy for HIV-1 infection. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy. October 30-November 2, 2004. Washington, DC. [Abstract H-1131]

4. Parikh UM, Koontz DL, Chu CK, et al. *In vitro* activity of structurally diverse nucleoside analogs against human immunodeficiency virus type 1 with the K65R mutation in reverse transcriptase. *Antimicrob Agents Chemother* 2005;49:1139-1144.
5. Landman R, Peytavin G, Descamps D, et al. Low genetic barrier to resistance is a possible cause of early virologic failure in once-daily regimen of abacavir, lamivudine, and tenofovir: the Tonus study. 11th Conference on Retroviruses and Opportunistic Infections. February 8-11, 2004. San Francisco. [Abstract 52]
6. Gallant J, Staszewski S, Pozniak A, et al. Efficacy and safety of tenofovir DF vs. stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *JAMA* 2004;292:191-201.
7. Klein D, Hurley LB, Quesenberry CP Jr, Sidney S. Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? *J Acquir Immune Defic Syndr* 2002;30:471-477.
8. Wohl DA, Cunningham C, Tien H-C, et al. A randomized, open-label clinical trial of omega-3-fatty acid (fish oil) supplementation along with diet and exercise in HIV-infected patients with hypertriglyceridemia. 11th Conference on Retroviruses and Opportunistic Infections. February 8-11, 2004. San Francisco. [Abstract 724]
9. Carter M. 'Dear Dr' letter issued about risks of using tenofovir and ddI together. [aidsmap.com](http://www.aidsmap.com). March 4, 2005. <http://www.aidsmap.com/en/news/32A4DCAC-1FFD-4563-8919-81C5F25B455D.asp>.
10. Moyle G, Maitland D, Hand J, et al. Early virological failure in persons with viral loads >10,000 copies/ml and CD4 count <200 cells/mm³ receiving didanosine/tenofovir/efavirenz as initial therapy: 12 weeks results from a randomised controlled trial. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy. October 30-November 2, 2004. Washington, DC. [Abstract H-566]
11. Podzamczar D, Ferrer E, Gatell JM, et al. Early virologic failure with a combination of tenofovir, didanosine and efavirenz. *Antivir Ther* 2005;10:171-177.
12. Leon A, Martinez E, Mallolas J, et al. Early virological failure in treatment-naïve HIV-infected adults receiving didanosine and tenofovir plus efavirenz or nevirapine. *AIDS* 2005;19:213-215.
13. Castillo AB, Tarantal AF, Watnik MR, Martin RB. Tenofovir treatment at 30 mg/kg/day can inhibit cortical bone mineralization in growing rhesus monkeys (*Macaca mulatta*). *J Orthop Res* 2002;20:1185-1189.
14. Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. *Clin Infect Dis* 2005;40:1192-1198.
15. For creatinine clearance of 30 to 49 mL/min, give 300 mg of TDF every 48 hours. For clearance of 10 to 29 mL/min, give 300 mg twice a week. For people on hemodialysis, give 300 mg every seven days or after a total of approximately 12 hours of dialysis.
16. Markowitz M, Mohri H, Mehandru S, et al. Infection with multidrug resistant, dual-tropic HIV-1 and rapid progression to AIDS: a case report. *Lancet* 2005;365:1031-1038.
17. Transmitted NNRTI-resistant virus tends to be as fit as nonresistant virus—or more fit—explained Douglas Richman (University of California, San Diego) at a CROI symposium. At the 2004 Resistance Workshop, Susan Little in Richman's lab reported significantly higher viral loads in people infected with NNRTI-resistant virus than in those infected with nonmutant virus, or with NRTI- or PI-resistant virus. High viral loads linked to NNRTI resistance, she speculated, "may contribute to the high frequency of transmitted NNRTI resistance." (Little SJ, Grant RM, Daar ES, et al. Transmitted NNRTI drug resistance is associated with higher steady-state viral load measures in untreated subjects with primary HIV infection. *Antiviral Ther* 2004;9:S58.) Transmitted virus in the New York case (see "GRIDLOCK," on page 138) bore the K101E and Y181I NNRTI mutations, conferring resistance to NVP. But the virus remained susceptible to EFV.
18. Webcasts from the 12th CROI are online for about a year after the conference at <http://www.retroconference.org/2005/Pages/webcasts.htm>. Besides Daniel Douek's talk (and many others), the Webcast library includes the complete session on the New York case of primary infection with multidrug-resistant, dual-tropic virus.
19. Mattapallil JJ, Douek DC, Hill B, et al. Massive infection and loss of memory CD4⁺ T cells in multiple tissues during acute SIV infection. *Nature* 2005;434(7,037):1,093-1,097.
20. Dion ML, Poulin JF, Bordi R, et al. HIV infection rapidly induces and maintains a substantial suppression of thymocyte proliferation. *Immunity* 2004;21:757-768.
21. CDC. Lymphogranuloma venereum among men who have sex with men—Netherlands, 2003-2004. *MMWR Morb Mortal Wkly Rep* 2004;53(42):985-988. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5342a2.htm>.
22. Russell S. Conference questions 'super-strain' of HIV: experts unsure if N.Y. case is unique or a general threat. *San Francisco Chronicle*. February 25, 2005. <http://www.aegis.org/news/sc/2005/SC050216.html>



Your connection
to AIDS thought
leaders:

www.iapac.org



ABSTRACTS

Journal of Infectious Diseases

Amplified HIV transmission and new approaches to HIV prevention

Cohen MS, Pilcher CD.

BACKGROUND: We estimated rates of human immunodeficiency virus (HIV)-1 transmission per coital act in HIV-discordant couples by stage of infection in the index partner. **METHODS:** We retrospectively identified 235 monogamous, HIV-discordant couples in a Ugandan population-based cohort. HIV transmission within pairs was confirmed by sequence analysis. Rates of transmission per coital act were estimated by the index partner's stage of infection (recent seroconversion or prevalent or late-stage infection). The adjusted rate ratio of transmission per coital act was estimated by multivariate Poisson regression. **RESULTS:** The average rate of HIV transmission was 0.0082/coital act (95 percent confidence interval [CI], 0.0039-0.0150) within ~2.5 months after seroconversion of the index partner; 0.0015/coital act within six to 15 months after seroconversion of the index partner (95 percent CI, 0.0002-0.0055); 0.0007/coital act (95 percent CI, 0.0005-0.0010) among HIV-prevalent index partners; and 0.0028/coital act (95 percent CI, 0.0015-0.0041) six to 25 months before the death of the index partner. In adjusted models, early- and late-stage infection, higher HIV load, genital ulcer disease, and younger age of the index partner were significantly associated with higher rates of transmission. **CONCLUSIONS:** The rate of HIV transmission per coital act was highest during early-stage infection. This has implications for HIV prevention and for projecting the effects of antiretroviral treatment on HIV transmission.

J Infect Dis 2005;191:1403-1409.

Journal of Acquired Immune Deficiency Syndromes

Managed care for AIDS patients: Is bigger better?

Solomon L, Flynn C, Lavetsky G.

CONTEXT: Medicaid provides funds for the majority of AIDS-related health care services in the United States. In an effort to stabilize steeply rising Medicaid costs, managed care programs are replacing traditional fee-for-service Medicaid services. **OBJECTIVE:** To assess the impact of patient volume on the quality of care received by AIDS patients within a state's Medicaid managed care system. **DESIGN:** Cohort study of AIDS patients who were enrolled in Medicaid at any time from July 1997 through December 1998. Patient charts were reviewed and abstracted. Additional information on the AIDS patients' mode of exposure, date of AIDS diagnosis, and vital status were obtained from the state's HIV/AIDS surveillance database.

PATIENTS AND SETTING: All known AIDS patients enrolled in the Maryland Medicaid managed care program were eligible. A total of 1,052 of 1,585 patient records were reviewed and analyzed. **MAIN OUTCOME MEASURES:** CD4 and viral load tests; preventive healthcare including screening for sexually transmitted infections; placement of tuberculin purified protein derivative (PPDs); hepatitis B and C screening; vaccination for hepatitis B; vaccination for pneumococcal pneumonia; Papanicolaou test screening; medication utilization including receipt of antiretroviral therapy and prophylaxis against *Pneumocystis carinii* pneumonia; case management services; and mortality. **RESULTS:** Healthcare quality indicators were examined by comparing the performance of clinical sites that saw a low volume of Medicaid AIDS patients per site (one to 15 patients), a medium volume (16 to 100 patients), and a high volume (101 to 500 patients). High-volume sites performed better on virtually all quality indicators. There were few differences in performance between low- and medium-volume sites. High-volume sites experienced a greater number of patient deaths; this was true after adjusting for potential confounders such as age, use of antiretrovirals, time since AIDS diagnosis, appropriate laboratory monitoring, and hospitalizations. **CONCLUSIONS:** Variations in quality of care for AIDS patients were observed in a statewide managed care system. These variations existed despite provisions to ensure quality care such as an enhanced payment system for managed care organizations providing services for AIDS. High-volume sites were more likely to adhere to Public Health Service guidelines and may offer the best opportunity to provide high-quality AIDS care.

J Acquir Immun Defic Syndr 2005;38(3):342-347.

Journal of General Internal Medicine

Caregiver burden and depression among informal caregivers of HIV-infected individuals

Pirraglia PA, Bishop D, Herman DS, et al.

BACKGROUND: Few studies have examined the factors associated with depression in informal caregivers of HIV-infected persons. **OBJECTIVE:** To investigate the relationship between depression and caregiver burden among informal caregivers of HIV-infected individuals. **DESIGN:** Cross-sectional study using baseline data from an ongoing randomized trial of a supportive telephone intervention. **PARTICIPANTS:** One hundred seventy-six dyads of HIV patients and their informal caregivers. **MEASUREMENTS:** Depression was defined as a Beck Depression Inventory >10. A Caregiver Strain Index >6 identified informal caregivers with a high caregiver burden. We used logistic regression to identify characteristics that were associated with depression in the informal caregiver. **RESULTS:** Informal caregivers were 42 years old (standard deviation [SD], 13), 53 percent female, 59 percent

nonwhite, and 30 percent had education beyond high school. Forty-seven percent of informal caregivers were the patient's partner, 18 percent a friend, and 35 percent a family member. Twenty-seven percent of informal caregivers had a high caregiver burden, and 50 percent were depressed. We found significantly greater odds of informal caregiver depression with high caregiver burden (odds ratio [OR], 6.08; 95 percent CI, 2.40 to 15.4), informal caregiver medical comorbidity besides HIV (OR, 2.32; 95 percent CI, 1.09 to 4.92), spending all day together (OR, 3.92; 95 percent CI, 1.59 to 9.69), having to help others besides the HIV patient (OR, 2.55; 95 percent CI, 1.14 to 5.74), and duration of the HIV patient's diagnosis (OR, 1.01 per month; 95 percent CI, 1.00 to 1.01). **CONCLUSIONS:** High caregiver burden was strongly associated with depression among HIV-infected individuals' informal caregivers, who themselves had difficult life circumstances. Informal caregivers of HIV patients may be in need of both mental health services and assistance in caregiving.

J Gen Intern Med 2005;2(34):1525-1497.

Sexually Transmitted Diseases

Increased incidence of squamous cell anal cancer among men with AIDS in the era of highly active antiretroviral therapy

Diamond C, Taylor TH, Aboumrad T, et al.

OBJECTIVE: We sought to determine if the introduction of highly active antiretroviral therapy (HAART) corresponded with changes in anal squamous cell cancer rates among men with AIDS. **STUDY:** We linked cancer registry data from 1988 to 2000 and AIDS registry data from 1981 to July 2003 for San Diego County. We defined 1991 to 1995 and 1996 to 2000 as the pre- and post-HAART periods, respectively. **RESULTS:** The annual incidence of invasive anal cancer increased from zero per 100,000 men with AIDS aged 25 to 64 years (95 percent confidence interval [CI], 0-226) in 1991 to 224 per 100,000 (95 percent CI, 102-425) in the year 2000. Pre-HAART, the average annual incidence of invasive anal cancer was 49 per 100,000 men with AIDS aged 25 to 64 years (95 percent CI, 16-114) versus 144 per 100,000 (95 percent CI, 93-212) post-HAART. The relative risk of invasive anal cancer among men with AIDS compared with men without known HIV/AIDS was 98 (95 percent CI, 36-264) pre-HAART and 352 (95 percent CI, 186-669) post-HAART. The increased incidence of anal cancer among men with AIDS resulted in an increase in the overall rate of anal cancer among men in San Diego County. **CONCLUSIONS:** The rising incidence of anal cancer among men with AIDS may be related to increased longevity with HAART and the consequent increased time at risk for the development of malignancy and/or the result of greater use of cytologic screening.

Sex Transm Dis 2005;32(5):314-320.

Delaying HCV treatment in HIV-positive patients

Michael Carter

Treatment for primary hepatitis C virus (HCV) infection is significantly less likely to be effective in coinfecting HIV-positive individuals, than in patients who are HCV-monoinfected, according to a study presented at the 11th Annual Conference of the British HIV Association (BHIVA) held April 20-23, 2005, in Dublin. In addition, investigators found that a significant number of HIV-positive patients spontaneously cleared HCV within the early weeks of infection and, accordingly, they recommend that if HCV treatment is initiated during acute infection, it should be delayed for 12 weeks.

Approximately 90 percent to 98 percent of individuals who are HCV-monoinfected achieve a sustained virological response after receiving anti-HCV therapy consisting of pegylated interferon (PEG-IFN) during the acute infection period. There are limited data about the effectiveness of this strategy in HIV-positive patients. It is known however that during acute infection with HCV, HIV-positive individuals have significantly higher HCV loads than individuals infected only with HCV.

In a prospective, open-label study, investigators from the Chelsea and Westminster Hospital in London evaluated the efficacy and safety of treatment for HCV during acute infection. Between 1997 and 2003, a total of 50 gay men with a mean age of 37 years were recruited for the study. Hepatitis C virus infection was confirmed by antibody testing. Hepatitis C viral load was measured at baseline, and at weeks four, 12, 24, 32, and 48.

If an individual was still HCV RNA-positive at week 12 they were treated with PEG-IFN and ribavirin (RBV) for 24 weeks. The primary endpoint of the study was the proportion of patients with a sustained

virological response to treatment (defined as a negative HCV PCR test at 48 weeks). Data on CD4 count, HIV viral load, liver function, side effects, and laboratory abnormalities were also gathered.

Of the 50 men included in the investigators' analysis, 12 (24 percent) spontaneously cleared HCV infection by week 12 and therefore did not receive anti-HCV therapy. Spontaneous clearance of HCV was significantly associated with a CD4 count above 500 cells/mm³ ($p=0.03$), and a lower HCV load ($p=0.04$).

Twenty-seven men accepted anti-HCV therapy, 16 (59 percent) of whom achieved a sustained virological response, and this was significantly associated with a lower mean peak alanine aminotransferase (ALT) level ($p<0.001$). Due to the small number of patients in the study, it was not possible to say if treatment outcome was significantly different between individuals infected with different HCV genotypes.

Median CD4 count fell by 58 cells/mm³ on the completion of anti-HCV therapy, and the level of HIV viral load did not change significantly. These are usual accounts for individuals receiving HCV treatment.

No deaths or new opportunistic infections occurred. But side effects were widely reported, the most common being depression and anxiety (33 instances) and flu-like symptoms (22 individuals). In addition, 13 cases of neutropenia and three cases of anemia were recorded. One patient had to discontinue his treatment because of side effects.

The investigators concluded that as only 59 percent of HIV-positive patients who are treated for acute HCV infection achieve a sustained virological response, this approach to the management of HCV is less effective in coinfecting patients than HCV-monoinfected individuals. ■

Reference

Gillece YC. Is the treatment of acute hepatitis C in HIV-positive individuals effective? 11th Annual Conference of the British HIV Association. April 20-23, 2005. Dublin. [Abstract 26]

Alimentary Pharmacology & Therapeutics

The safety of pegylated interferon alpha-2b in the treatment of chronic hepatitis B: Predictive factors for dose reduction and treatment discontinuation

van Zonneveld M, Flink HJ, Verhey E, et al., for the HBV 99-01 Study Group

BACKGROUND: Treatment with interferon-alpha has been shown to be effective in one third of hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (HBV) patients, but is clinically associated with relevant adverse events. **AIM:** To investigate the safety of pegylated interferon (PEG-IFN)-alpha-2b in 300 HBeAg-positive patients with compensated liver disease. **METHODS:** Patients were treated with PEG-IFN alpha-2b for 52 weeks combined with either lamivudine (3TC) 100 mg/day or placebo. Pegylated interferon alpha-2b was administered for 100 µg once a week for 32 weeks; thereafter, the dose was reduced to 50 µg once a week. Adverse events and their effect on study medication were reported at monthly visits in a standardized way. **RESULTS:** The most frequently reported side effects were flu-like syndrome (68 percent), headache (40 percent), fatigue (39 percent), myalgia (29 percent), and local reaction at the injection site (29 percent). These symptoms typically occurred within the first month of therapy and subsided during the course of therapy. Neutropenia and thrombocytopenia induced by PEG-IFN alpha-2b increased the risk of infections and bleeding complications, but these complications were rare and mild. The frequency of all side effects was not different between patients treated with PEG-IFN alpha-2b combined with 3TC or placebo. In 69 (22 percent) patients the dose of PEG-IFN alpha-2b was reduced prematurely. Of these dose reductions, 36 (52 percent) were because of neutropenia. Therapy was discontinued in 28 (8 percent) patients. The most frequent reasons for early discontinuation were psychiatric side effects (depression, psychosis) and flu-like symptoms. Multivariate Cox regression analysis showed that low neutrophil count at baseline and cirrhosis were independent predictors of dose reduction or therapy discontinuation. **CONCLUSION:** We conclude that in patients with chronic HBV and compensated liver disease prolonged PEG-IFN alpha-2b therapy is safe, and that pre-existent cirrhosis and neutropenia are the most important predictors of dose reduction or early treatment discontinuation.

Aliment Pharmacol Ther 2005;21(9):1163-1171.

Editor's Note: This article is reprinted with permission from www.aidsmap.com, and was first e-published April 26, 2005.



IN THE LIFE



Ojuluwayo Joshua

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

This month, *IAPAC Monthly* is proud to feature Ojuluwayo Joshua, Director of Youth On Line at the Grand Hospital in Lagos, Nigeria.

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

The fear of facing obstacles is the beginning of failure, but approaching the obstacle is the beginning of success. Success does not occur by chance.

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

Soccer and problem-solving.

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

I would live in Nigeria, because there you will be strong, and you will be ready to face the unusual.

Who are your mentors or real life heroes?

Thomas Alva Edison.

With what historical figure do you most identify?

Adekunle Fajuyi, one of the brave Nigerian military men who died in the course of defending former President Aguiyi Ironsi.

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

Author: Wole Soyinka. Painter: Daniel Festus.

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

In the days of Jesus Christ.

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

A mathematician.

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

The greatest achievement is the formation of the United Nations. The greatest failure is the invention of atomic weapons, and other weapons of mass destruction.

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

Most present-day health problems will be solved, and the issue of poverty in Africa, coupled with dictatorships, will be eradicated. ■



THE GRACE IN ROSEBANK

Set in the heart of stylish Rosebank, The Grace is an ideal choice for guests seeking a sophisticated city hotel with the highest levels of service and luxury, as well as the personal charm found only in smaller establishments. The hotel's 73 bedrooms are ideally positioned to provide personal, unobtrusive hospitality. They breathe sumptuous yet understated elegance, set to standards of excellence dating back to an era of gracious living and dedication to detail.

The Dining Room—with its excellent service and imaginative cuisine, will provide a memorable dining experience. Indulge yourself at The Spa, where we offer a range of luxurious health and spa treatments, or relax under African skies on the roof garden and pool terrace, where light meals, teas and drinks are served high above the hum of the streets below.

*The Grace is more than a fine hotel...
It is a gracious home.*

IAPAC Members enjoy a special discounted rate. Mention your membership in IAPAC when booking your reservation.



Reservations:

The Grace in Rosebank
54 Bath Avenue, Rosebank, 2196
P.O. Box 2639, Saxonwold, 2132
South Africa

Tel: +27 11 280 7200

Fax: +27 11 280 7474

Email: graceres@the-grace.co.za

Web Site: www.the-grace.co.za

GDS codes:

Amadeus LX JNB TGR

APOLLO/GALILEO LX 87237

SABRE LX 40367

WORLDSPAN/ABACUS/

SAHARA LX JNBGR





SAY ANYTHING

e
[W]e know that with the right policies and actions rapid progress is possible, and the success of the better performing regions and countries, including in sub-Saharan Africa, provides hope for others.

James Wolfensohn, outgoing World Bank President, in an April 16, 2005, Agence France Presse report, in which he stated that the year 2005 is the “last opportunity” to take the steps necessary for Africa to meet the Millennium Development Goals set by the United Nations (UN) in 2000. Those goals include halving global poverty, increasing efforts against endemic diseases such as HIV/AIDS and tuberculosis, and providing additional access to education. Although the goal of slashing poverty should be accomplished due to the economic growth of India and China, the remaining goals still need global cooperation if they are to be met. Sub-Saharan Africa, in particular, has experienced a decline in these indicators.

e
The growing number of people who need HIV medications, and rising drug costs, continue to exceed available resources.

Jennifer Kates, the Kaiser Family Foundation’s Director of HIV Policy, in an April 20, 2005, Reuters article discussing a new report compiled by the Kaiser Family Foundation and the National Association of State and Territorial AIDS Directors (NASTAD). The report found that more than 600 low-income HIV-positive patients in 11 states are on waiting lists for medication assistance through state AIDS Drug Assistance Programs (ADAPs). In 2004, additional funding by states, drug rebates, and higher levels of federal assistance allowed 38 states to permit more people to receive benefits through

ADAPs. In 11 states, however, a total of 627 people were put on waiting lists. Ten additional states took cost-cutting measures, including limiting drug benefits.

e
Ten years ago, you weren’t finding any incidence of HIV among migrants in California, so this is significant.

Maria Hernandez, a researcher for the Universitywide AIDS Research Program (UARP) in the University of California (UC) system, in an April 20, 2005, Associated Press story about a UC study of HIV/AIDS risk among migrant farm workers. The State of California has an estimated 1.3 million migrant laborers, among whom previous studies have documented a fairly high amount of risk behavior but not many cases of HIV. However, the current study has turned up five cases of HIV among its 781 study participants, drawn from both urban and rural populations. Another recent study, conducted at the University of California, San Diego, found that pregnant women in labor in Tijuana, Mexico, had a four times greater risk of being HIV-positive than did women in similar groups in either the United States or Mexico.

e
Unfortunately, we lost some of our patients who were waiting.

Isaac Adewole, Provost at the University of Ibadan School of Medicine in Nigeria, quoted in an April 24, 2005, Boston Globe article regarding Harvard University’s delay in spending funds it was awarded through the US President’s Emergency Plan for AIDS Relief (PEPFAR). Four institutions were awarded funds through PEPFAR in February 2004, including Harvard University,

Columbia University, the Catholic Relief Services, and the Elizabeth Glaser Pediatric AIDS Foundation. Except for Harvard University, all the institutions began implementing their programs the following month. Harvard University began ordering antiretroviral drugs for its programs in September 2004, and the drugs did not arrive in Nigeria until November/December 2004. According to Harvard University Provost Steven E. Hyman, during the intervening months, the university’s President, Lawrence H. Summers, and he were reviewing potential legal threats with the antiretroviral therapy scale-up programs as they were originally conceived.

e
This sends the wrong message to young people: “Here are the syringes, go use them.”

Alistair Barros, President of the Australian Families Association of Queensland, Australia, in an April 17, 2005, Sunday Mail article regarding the Queensland Health Department’s installation of needle vending machines in five area hospitals in a trial program set to run through the end of 2005. The machines dispense five fresh syringes and a disposal container for US\$1.55. The agency said the effort to dispense clean needles will cut down on needle sharing and reduce the spread of HIV and hepatitis C. Some in the community, however, are outraged by the effort. Barros said the government’s harm-reduction approach to drugs is not working. Five years ago, a similar move by Victoria’s health department to install needle vending machines throughout Melbourne was dropped after public outcry. And, New South Wales health authorities last year scrapped a plan to replace a needle-exchange van with a vending machine in Sydney.

WHY DOES ANASTACIA WEAR THE BRACELET?

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

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