

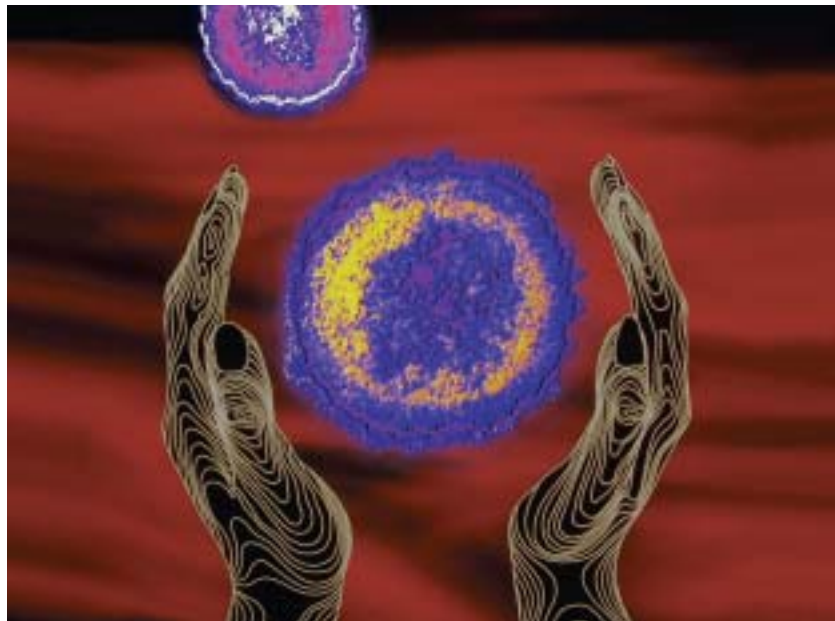
March 2002 VOL. 8, NO. 3

IAPAC

MONTHLY

**New antiretroviral tactics,
new antiretrovirals,
old side effects**





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COVER STORY

New antiretroviral tactics, new antiretrovirals, old side effects

Mark Mascolini

Opinion on the timing—and, by implication, the merits—of antiretroviral therapy could hardly have been more divided than in a crowd of HIV clinicians attending an interactive session at the rescheduled 41st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) held December 16-19, 2001.

More than one study directly addressed these persisting questions.

And, other work zeroed in on resistance, toxicity, and treatment breaks.

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

No acceptable excuse for inaction

José M. Zuniga

One of the more lamentable paradoxes of our modern world is that while the marvels of technology and medicine yield potential to significantly enhance both the quality and duration of life, those in positions of political import often fail to harness the will and conscience necessary to make the most of these advances. Most of us remain incessantly bewildered by and horrified at the suffering and death that, sadly, is often caused not by want of either knowledge or means, but rather as a direct and indirect consequence of political complacency and bureaucratic rigidity.

The global AIDS community recently has watched as complacency and rigidity has foamed forth in South Africa, evidenced in the rhetoric employed by the country's sitting government as it responds to demands that nevirapine be supplied for administration to HIV-positive pregnant women. Nevirapine—a single dose of which halves the likelihood of an HIV-positive woman transmitting the virus to her child at birth—has thus far been unavailable through national public health services.

In response to the government's failure to supply nevirapine, a group of approximately 200 South African physicians—many of whom have been paying for and supplying the drug to women out of their own pockets—has cooperated with South Africa's Treatment Action Campaign (TAC) to pressure the government to open up access to the drug. The debate over nevirapine seems to have brought them to an impasse with the government.

Since assuming leadership of the country in 1999, President Thabo Mbeki and his government have experienced numerous AIDS-related political challenges. From the brouhaha following his questioning

of AIDS' causal agent, to a government-mounted defense to defeat an eventually retracted lawsuit meant to limit its ability to import generic drugs, the national political response has been spotty, at best. The government's political response to this new dilemma has been far worse.

A December 2001 high court ruling that the government begin dispensing nevirapine to all suitable HIV-positive women in the country has only produced further controversy. And, despite national and international pressure, Mbeki's government appears to be seeking reprieve from its duty by resorting to the politics of rhetoric.

The government had previously committed itself to putting in place mechanisms and regulations necessary to facilitate the import of generic AIDS drugs, and has now been further compelled by the high court to design a comprehensive strategy for reducing mother-to-child transmission of HIV. Yet, nothing to date has been forthcoming.

Petitioning the high court to reconsider its recent ruling on nevirapine access, the government stated both that numerous provinces can simply not afford to supply nevirapine, and that to give attention to HIV/AIDS concerns over and above other competing public health concerns would be unjust. These defenses only underscore an inexcusable resort to rhetoric instead of forthrightness.

In South Africa, a country in which an estimated 4.7 million people are currently infected with HIV—the highest national incidence rate in the world—HIV/AIDS constitutes a public health emergency, the gravity of which cannot be overstated. Thousands of South African children, women, and men are infected with HIV each day, and thousands die each week from AIDS-related illnesses. The arguments

put forth by the government, therefore, constitute no less than an implicit death sentence for those living with AIDS.

My words here are not meant to reflect a concentrated and exclusive attack on South Africa's government. In the dilemma it faces, as well as in its equivocal response to this critical public health emergency, Mbeki's government has many partners on the global stage, both within and outside of the African continent. Rather, directing my gaze upon the epidemic of unparalleled national proportions that South Africa is faced with, this serves both as a call to conscience and a plea for action.

That the South African government may not have at its immediate disposal the funds to fully open up access to nevirapine and other antiretroviral drugs is a legitimate argument. So, too, is the point that the country faces other pressing public health issues. These, however, are not acceptable excuses for inaction. Indeed, there is no acceptable excuse for inaction.

South Africa's government must seek creative funding schemes and establish ethical and strategic alliances to expand and sustain drug access. And, where lacking in the capacity to fulfill its public health functions, the government must reach out to organizations that have at their disposal the energy, knowledge, and networks to provide critical technical assistance and capacity building.

Ultimately, the decision about whether to commit to such action is one that will record, for posterity, the true character of President Thabo Mbeki and his government—and, by natural extension, that of the citizens they govern. ■

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



TAC, MSF import generic AIDS drugs into South Africa

In defiance of patent laws, three members of the Treatment Action Campaign (TAC) returned to South Africa from Brazil on January 28, 2002, carrying generic, Brazilian-manufactured versions of AIDS drugs for use in a Médecins sans Frontières (MSF) treatment program in Khayelitsha, a township outside Cape Town.

At a press conference the next day, TAC and MSF representatives told reporters that the drugs carried from Brazil were the second shipment of Brazilian drugs. Further, they stated that as of January 2002, 50 people living with HIV/AIDS in Khayelitsha were already taking generic zidovudine (AZT), lamivudine (3TC), and nevirapine.

“Last week in Brazil, we saw what happens when a government decides to tackle HIV/AIDS. The Brazilians’ decision to offer universal access to antiretroviral therapy, even in the poorest areas of the country, is keeping tens of thousands of people alive,” said TAC’s Zackie Achmat. “Central to the success of Brazil’s AIDS program is their willingness to do anything necessary to source the lowest cost quality [antiretrovirals]. The South African government should pursue compulsory licensing to ensure that generic antiretrovirals can be produced and/or imported in South Africa.”

Despite the South African government’s refusal to provide antiretroviral treatment, three clinics run by MSF within the government primary healthcare centers offer a comprehensive package of services to people living with HIV/AIDS, including antiretroviral therapy. This project is part of an agreement between MSF and the government of the Western Cape, signed two years ago with the express intent to test the feasibility of antiretroviral therapy provision.



According to MSF, these clinics, located in Khayelitsha, were opened in April 2000 and have provided treatment for opportunistic infections for over 2,300 people living with HIV/AIDS. In May 2001, combination antiretroviral therapy was introduced for a group of 85 people in advanced stages of HIV disease—50 of them are receiving generic antiretroviral drugs. MSF asserts that using generic antiretroviral drugs offers the possibility of treating twice the number of people with the same amount of money.

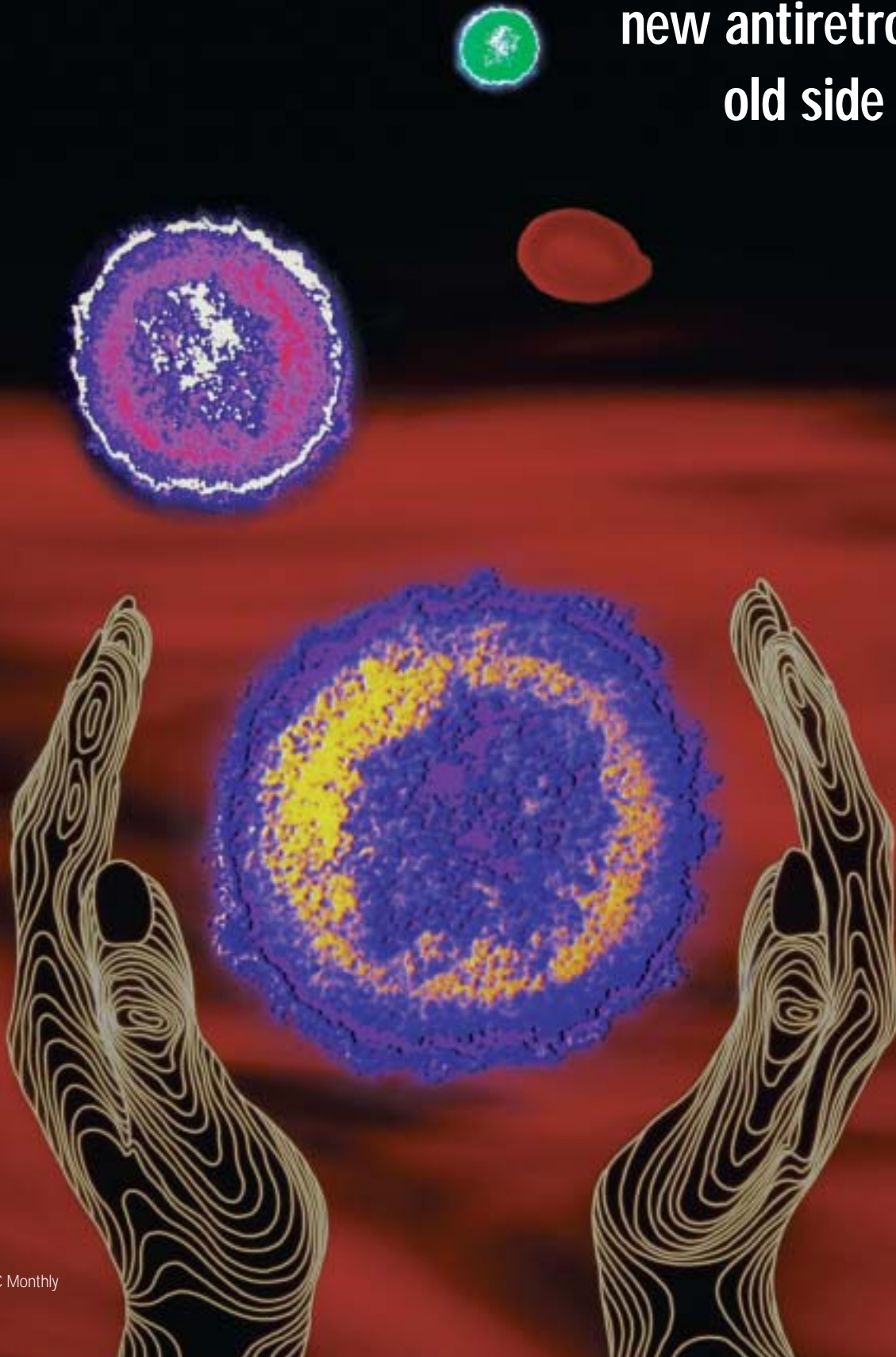
“Our project shows that antiretroviral therapy is feasible in a resource-poor setting, contrary to those who insist that poor Africans are not able to successfully take these drugs. Patients who were critically ill are now returning to their normal lives,” said Eric Goemaere of MSF South Africa. “We have seen firsthand that these drugs

can be used safely and effectively here in South Africa. As medical professionals, it is our duty to offer these benefits to as many patients as possible.”

According to the Associated Press, GlaxoSmithKline, which holds the patents for both zidovudine and lamivudine, has said that it will respond to patent infringements on a case-by-case basis. And, nevirapine’s manufacturer, Boehringer Ingelheim, has announced that it has yet to decide how to respond to the TAC-MSF importation of a generic version of its drug. ■

Editor’s Note: This report was compiled from numerous sources, including the Associated Press, The Guardian (UK), and a joint press statement from Médecins sans Frontières and the Treatment Action Campaign.

New antiretroviral tactics, new antiretrovirals, old side effects



Opinion on the timing—and, by implication, the merits—of antiretroviral therapy could hardly have been more divided than in a crowd of HIV clinicians attending an interactive session at last December's ICAAC. When Brian Gazzard (Chelsea and Westminster Hospital, London) posed the session's first case on when to start antiretroviral therapy, the audience split almost straight down the middle. Gazzard described a healthy 29-year-old man, seropositive for three years, with a CD4⁺ count of 410 cells/mm³ and a viral load of 98,000 copies/mL. A bare majority, 53 percent, voted to delay therapy, while the remaining 47 percent said start.

The next speaker, Daniel Kuritzkes (University of Colorado, Denver) elicited an even closer vote with the case of a 21-year-old asymptomatic man who started zidovudine (AZT), lamivudine (3TC), and nelfinavir with a CD4⁺ count of 362 cells/mm³ and a viral load of 33,000 copies/mL. After the viral load fell below 50 copies/mL and the CD4⁺ crested above 500 cells/mm³, the 3TC-resistant 184V mutation arose and virus bustled back into circulation. After posing five alternative regimens for consideration, Kuritzkes simplified the task by asking how many would just stop therapy altogether: 49 percent said yes, and 51 percent no.

Since the interactive quiz came as the meeting's last HIV session, the several hundred attendees had more than one study to mull when formulating their answers. There had been the usual heap of reports on antiretroviral side effects, containing only a few shards of good—or at least neutral—news. There had been a smattering of data on new antiretrovirals, and none of those findings suggested a sea change in navigating HIV therapy. There had been one report on ugly rates of drug resistance in the US.

There had even been two studies—one big, one small, both convincing—that directly addressed Gazzard's and Kuritzkes' questions.

Start later—and stop if you started too soon?

More than one cohort study published last year found no virologic^{1,2} or survival³ benefit in starting treatment when the CD4⁺ quotient still sits above 350 cells/mm³. In

fact, the clinical endpoint study in this triad³ discerned no survival advantage for starting above 200 cells/mm³.

Inveighing against blanket recommendations on CD4⁺ start signals is easy. In his interactive talk Brian Gazzard, hardly an early start hard-liner, raised the concern that delaying treatment may open the door to neoplastic opportunists. And he underscored that concern with data. In a review of people at Chelsea and Westminster Hospital in whom HAART kept CD4⁺ counts from sinking under the 350-cell line, the incidence of non-Hodgkin's lymphoma measured 0.7 per 100 person-years, the same rate as in the general population. But in people whose CD4⁺ counts had drifted below 350 cells/mm³ before HAART began, the rate was 10 per 100 person-years.

Still, the snares and snarls of multidrug therapy have convinced many to play a waiting game. As Gazzard observed during his interactive quiz, three years ago a hefty majority of US clinicians would have urgently urged antiretrovirals for that person with a 98,000-copy viral load. And some of those who favored starting therapy for such a person when ICAAC began probably changed their minds after a mega-cohort analysis by Matthias Egger (University of Bristol) [abstract LB-18].

Amassing data on 12,574 treatment-naive people starting at least three antiretrovirals, Egger found that age over 50 years, a history of injecting drug use, an AIDS diagnosis at baseline, a starting viral load above 100,000 copies/mL, and a baseline CD4⁺ count below 200 cells/mm³ raised the risk of disease progression or death within three years.

These are only the broad strokes. In an intent-to-treat analysis that did not account for regimen changes or treatment interruptions, Egger reckoned progression risks one, two, and three years after starting treatment for 80 different risk strata. And he showed restraint in stopping at 80, because he mixed only five variables in his model:

- Age under 50 years versus 50 and older
- Injecting drug use or not
- AIDS diagnosis (CDC stage C) versus CDC stage A or B
- Baseline CD4⁺ counts of 0 to 49, 50 to 99, 100 to 199, 200 to 349, and more than 349 cells/mm³

- Baseline viral load less than 3 logs (1,000 copies/mL), 3 to 3.99 logs, 4 to 4.99 logs, 5 logs (100,000 copies/mL) or higher

Since ICAAC's late-breaker format (not to mention peer-reviewed journals) couldn't accommodate Egger's 240 separate analyses, he offered only highlights. Egger found little overall difference in progression between people who started treatment with CD4⁺ counts at or above 350 cells/mm³ and those who started with 200 to 349 cells/mm³. About 95 percent in both groups survived for three years, compared with about 75 percent who started with sub-50 CD4⁺ counts. Setting the progression risk at 1 for people starting with fewer than 50 cells/mm³, Egger calculated a risk of 0.75 for those starting with 50 to 99 cells/mm³, 0.53 for those starting with 100 to 199 cells/mm³, 0.25 for those starting with 200 to 349 cells/mm³, and 0.18 for those starting with more than 349 cells/mm³.

Looking only at people younger than 50 who never injected drugs or had an AIDS diagnosis, Egger found that starting above or below 100,000 RNA copies/mL did not affect three-year progression for people starting with 200 to 349 cells/mm³ or for those with more than 350 cells/mm³ (Table 1). Although progression rates were marginally faster in those with starting loads above 100,000 copies/mL, the confidence intervals overlapped those of people starting with lower viral loads and rendered the difference statistically nonsignificant.

Egger also failed to discern a progression difference between people who began treatment with a nonnucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), or two PIs. He noted, though, that the intent-to-treat analysis ignored regimen switches and may mask subtle differences between drug classes.

Most of these data on factors that influence starting HAART emerged only in the past couple of years. So clinics are full of people who started treatment with CD4⁺ counts in the 400s and viral loads under 5 logs, like Gazzard's hypothetical 29-year-old (described in the preceding section). Now lots of nonhypothetical HAART veterans with high CD4⁺ counts and clamps on viral replication want to know if they can stop. Joel Gallant and Michelle Parish

Table 1. Three-year progression (%) based on starting CD4+ count and RNA in a subset* of a 13-cohort study

Baseline CD4+ count (cells/mm ³)									
<50 with RNA log:		50 to 99 with RNA log:		100 to 199 with RNA log:		200 to 349 with RNA log:		≥350 with RNA log:	
≥5	<5	≥5	<5	≥5	<5	≥5	<5	≥5	<5
20.3	18.8	16.1	12.5	12.1	9.3	6.1	4.7	4.4	3.4

*The subset includes people younger than 50 years old with no history of AIDS or injecting drug use. The entire cohort includes 12,574 people and more than 24,000 person-years of follow-up.

Source: Matthias Egger, abstract LB-18.

(Johns Hopkins University, Baltimore) tried to answer that question with a chart review, and their provisional answer is perhaps, at least in certain circumstances [abstract 673].

They looked at 62 people who all started HAART without an AIDS diagnosis and with a CD4+ count above 200 cells/mm³ then stopped, with their clinicians' advice, for diverse reasons: 44 percent quit because recent guidelines no longer recommend antiretrovirals for people who started when they did; 18 percent stopped because of toxicity; and another 18 percent quit because of poor adherence.

At last report, 46 (74 percent) have not resumed therapy for an average 64 weeks, while 16 (26 percent) did start again after an average 33-week hiatus. Thirteen of the 16 returnees did so because of a viral load rebound, a CD4+ drop, or both. One person started because of a symptomatic rebound after stopping HAART. No one in either group suffered an opportunistic infection or malignancy. All 15 of the 16 restarters still in follow-up have lowered their viral load to undetectable levels or are on their way down again.

Four factors distinguished people who resumed therapy from those who didn't: a lower pre-HAART CD4+ nadir, a lower CD4+ count when they began HAART, the RNA bounce during the drug break, and maximum pre-HAART viral load (Table 2). But in a multivariate analysis, only the maximum pre-HAART viral load foretold the need to resume therapy, raising the odds of resuming 2.3 times ($P = 0.036$). Restarters and nonrestarters didn't differ in HAART duration or in their maximum CD4+ gain during HAART.

Although retrospective, this study holds obvious interest for HAART takers and planners alike. The findings could be the first palpable buttress to pulsed therapy—a strategy now being tested prospectively. Unlike treatment interruptions with fixed

intervals off drugs, like the recently reported one-week-on-one-week-off tactic,⁴ pulsed therapy would simply withdraw antiretrovirals until the CD4+ tally drifted down to some set level, such as 250 or 350 cells/mm³. In theory that could spare people the monetary and toxic cost of continued therapy. In the Johns Hopkins cohort, for example, two of nine people with lipodystrophy while taking antiretrovirals and one of four with lipohypertrophy enjoyed some improvement after they stopped their meds. Lipid levels also receded.

But Gallant noted an irksome irony in these findings. In this group the best candidates for pulsed treatment breaks were those with high CD4+ counts and low viral loads before starting HAART—precisely those people who rarely start HAART these days because of amended 2001 guidelines. If one reserves pulsed therapy for people like those who responded well at Johns Hopkins, Gallant observed, the candidate pool is drying up fast.

Resistance clouds future, but one silver lining seen

How many people in the US with a detectable viral load and taking antiretrovirals have resistant virus? No one knows, of course, but a big sample population and some fancy number noodling suggest that the answer, in 1999, was 78 percent.

Douglas Richman (University of California, San Diego) dispensed that unhappy datum in collaboration with researchers from the HIV Cost and Service Utilization Study (HCSUS), which tracks a cohort selected to represent all HIV-infected people in the US under medical care in 1996 [abstract LB-17].

The HCSUS team started with 1,906 plasma samples and set aside 698 because they came from people with viral loads under 500 copies/mL. Richman enlisted ViroLogic phenotypers to assess drug susceptibility in the remaining 1,208 isolates

from people with viral loads above 500 copies/mL who were being treated in 1996 and survived through 1999. From that sample, ViroLogic could phenotype 1,080 isolates, which statisticians figured represent 117,976 people taking antiretrovirals during those years. The researchers called an isolate resistant to didanosine (ddI) or stavudine (d4T) if it proved 1.7-fold more resistant than wild-type virus, resistant to abacavir at a cutoff above 4.5-fold, and resistant to all other drugs at a cutoff above 2.5-fold.

With those criteria, 78 percent of the 1,080 viremic people in medical care and with resistance test results had virus resistant to at least one antiretroviral. A disheartening 51 percent of these isolates proved resistant to drugs from at least two antiretroviral classes (Table 3). Among all 1,906 viral isolates, including the 698 from people with viral loads under 500 copies/mL, the resistance rate measured 50 percent. But Richman called that an underestimate, because it assumed all people with sub-500 viral loads had drug-susceptible virus. In fact, many people with such low loads may have archived mutants or even freshly evolving mutations spawned during recondite viral replication.

Nadir CD4+ count before therapy predicted resistance, but T-cell numbers when the sample was taken did not. Among people with a CD4+ nadir under 50 cells/mm³, 90 percent had resistant virus, as did 84 percent of those with an AIDS diagnosis. Other factors that favored resistance all signal better access to care and hence to antiretrovirals: male gender, white non-Hispanic ethnicity, exposure to HIV via gay sex, more education, and private insurance. People living in the Midwest had a lower resistance risk.

At least two aspects of the study's design may soften the blow of these brutal data. Session cochair Scott Hammer (Columbia University, New York) noted that many people being treated in 1996, like those in this sample, probably already had single or double nucleoside (NRTI) experience and so had a big head-start in the resistance race. Others observed that the 2.5-fold cutoff is low for NNRTIs. For example, Virco's so-called biologic cutoffs for efavirenz and nevirapine are 6.0 and 8.0 respectively. As a result, this analysis probably called many isolates resistant to NNRTIs when others would call them susceptible.

Table 2. **Differences between people who resumed or did not resume HAART after a break**

	Resumed HAART	Didn't resume HAART	P
n	16	46	
Met 2001 DHHS guidelines for starting HAART	8	12	0.07
Pre-HAART CD4+ count (cells/mm ³)	389	442	0.03
CD4+ count at start of HAART (cells/mm ³)	389	479	0.02
Mean viral load on HAART (copies/mL)	1,930	906	0.137
Mean viral load during break (copies/mL)	122,533	22,620	<0.001

DHHS = US Department of Health and Human Services.
Source: Joel Gallant, abstract 673.

But no one tried to put a cheery spin on these numbers. Everyone already knew that many people starting treatment in the 1990s and trading regimens ever since would harbor lots of resistant virus. The only question was whether the rate should be called rampant or runaway. The HCSUS team did not prescribe an adjective but, within the limits of any such study, they did confirm suspicion.

Richman added one other worrisome result. Among people in this cohort who said they never took an antiretroviral, 20 percent had resistant virus. Drug histories may be a flimsy screen for resistance, Richman argued. Resistance testing for all people beginning therapy may deserve more scrutiny.

Another study found almost exactly the same resistance rate in chronically infected, treatment-naïve people [abstract 1747]. H. Balaguera (Boston Medical Center) and colleagues at other Boston sites documented resistant genotypes in 16 of 88 untreated individuals (18 percent). Twelve had NRTI-linked mutations, four had NNRTI mutations, three had PI mutations, and two had multiclass mutations. People starting treatment with resistant virus took longer to corral their unruly virus. But after 48 weeks, all 12 people with resistant HIV who started therapy had a viral load under 50 copies/mL. In contrast, among 47 people who started treatment without resistance, only 27 (57 percent) had a 48-week viral load under 50 copies/mL.

Insulin resistance with nelfinavir

Suppose a 53-year-old man with a nine-year history of asymptomatic HIV infection walks into your office, suggested Chelsea and Westminster's Brian Gazzard at ICAAC's interactive voting session. His CD4+ count was 310 cells/mm³ a year ago;

now it's 190 cells/mm³. He also has a family history of heart disease and hyperlipidemia poorly controlled by diet and exercise. What would you do?

- Start a PI regimen.
- Start an NNRTI regimen.
- Delay antiretrovirals until he reins in the lipids.

If you're like this ICAAC audience, the answer is easy. Only 7 percent would delay HAART. Only 9 percent would use a protease drug. Everyone else opted for an NNRTI.

But which NNRTI? Gazzard noted that efavirenz keeps pace with PIs not only in antiviral potency, but also in sculpting abnormal lipid profiles. Meanwhile, some research shows nevirapine framing an antiatherogenic profile.⁵ On the other hand, three cohort studies found better virologic responses to efavirenz than to nevirapine in first-line regimens.⁶⁻⁸

Yet for someone like Gazzard's 53-year-old with his fractious lipids, most would probably lean toward nevirapine. Certainly the PIs' collective metabolic record has gone from grim to grimmer in the past year. Work unveiled at October's Lipodystrophy Workshop implicated indinavir, ritonavir, and amprenavir in rapid insulin resistance, perhaps mediated by a glucose transporter called GLUT4.^{9,10} Other research suggested that central fat buildups, a long-term consequence of PI therapy, independently contribute to insulin resistance.¹¹ The apparent mechanism is increased lipolysis, the dumping of fat into the circulation. At ICAAC, a cell study suggested how nelfinavir also does its part to inspire insulin resistance.

Klaris Riesenber and colleagues (Ben-Gurion University, Beer-Sheva, Israel)

Table 3. **Resistance rates* in 1,080 viremic people in care from 1996 through 1999**

Antiretroviral drug or class	Resistant isolates (%)
Any drug	78
NRTIs	70
PIs	42
NNRTIs	31
Two or more classes	51
Three classes	14

*Resistance cutoffs were set at >1.7-fold for ddI and d4T, >4.5-fold for abacavir, and >2.5-fold for all other antiretrovirals.
Source: Douglas Richman, abstract LB-17.

had already reported that subjecting 3T3-L1 adipocytes (fat cells) to nelfinavir inhibits insulin-stimulated glucose uptake and boosts lipolysis.¹² The ICAAC study exposed adipocytes to increasing concentrations of nelfinavir over 18 hours in an attempt to find out why [abstract 227].

This work confirmed that nelfinavir increases basal lipolysis and derails insulin-stimulated glucose transport in fat cells, but the mechanism appeared to be novel. Rather than interfering with GLUT4, nelfinavir impaired insulin-stimulated serine phosphorylation by protein kinase B, p70 S6 kinase, and ERK1/2, findings suggesting to Riesenber that the PI activates a common phosphatase. Pretreating or cotreating the cells with the insulin sensitizer troglitazone inhibited nelfinavir's activation of basal lipolysis but did not bring insulin-stimulated glucose transport back in line. (Troglitazone has been pulled from the market, but pioglitazone and rosiglitazone are being studied in HIV-infected people with insulin resistance.) Whatever the why and wherefore behind nelfinavir's impact on glucose transport, it appears that this drug could also contribute to lipodystrophy via insulin resistance.

Antiretrovirals and classic cardiovascular risk factors

The question on everyone's mind is whether antiretroviral meddling with glucose and lipids will nurture an epidemic of cardiovascular disease as people take their anti-HIV drugs year after year. The prospective, multicohort D:A:D¹³ study aims to find out and already has 20,421 HIV-infected people on its rolls. Rainer Weber (University Hospital Center, Zurich)

Table 4. Odds ratios* for total cholesterol above 6.2 mmol/L in 20,421 with HIV infection

Variable	Odds ratio
Treatment with NRTIs only	0.9
Treatment with NNRTIs	1.9
Treatment with PIs	2.48
Triple-class treatment	5.83
NRTI exposure per year	0.99
NNRTI exposure per year	1.32
PI exposure per year	1.3

*The multivariate analysis controlled for age, gender, smoking, and family history of heart disease.

Source: Rainer Weber, abstract 1326.

reported at ICAAC that treatment with either PIs or NNRTIs inflates the odds of hypercholesterolemia [abstract 1326]. But Weber had no clinical endpoint data, and the NNRTI link remains ill defined.

About 12 percent of the cohort had no antiretroviral experience. Nearly all of the others took NRTIs for a median 3.6 years, while 73 percent used PIs for a median 2.8 years, and 40 percent took an NNRTI for a median 1.3 years. About 7 percent were taking a triple-class regimen. The risk model D:A:D statisticians devised includes age (median 39 years), gender (25 percent female), smoking (by more than 50 percent), and family history of heart disease (in 12 percent). Higher CD4⁺ count and lower viral load correlated with higher total cholesterol. Treatment with NRTIs alone didn't influence the odds of having a cholesterol reading above 6.2 mmol/L, but treatment with NNRTIs, PIs, and three-class regimens did (Table 4). Each year of treatment with NNRTIs and PIs also raised the odds of hypercholesterolemia.

What the D:A:D team has not yet reported is how many of the 40 percent taking NNRTIs were taking efavirenz and how many nevirapine, a crucial bit of datum given the different impact these drugs have on lipids. And D:A:D number crunchers have yet to distinguish NNRTI takers who are PI naive from those who traded a PI for an NNRTI.

Sizing up the D:A:D results so far, session cochair William Powderly (Washington University, St. Louis) proffered two interpretations: The slightly more sunny possibility is that certain people are predisposed to hypercholesterolemia, and antiretroviral

Table 5. Triglycerides in people with or without lipodystrophy after 24 months of >95% adherence

Treatment month	TG (mg/dL) in people without lipodystrophy	TG (mg/dL) in people with lipodystrophy	P
Baseline	111	123	NS
3	142	178	NS
6	132	205	0.015
12	146	267	0.003
18	151	358	0.0001
24	154	295	0.0001

NS = not significant.

Source: A. Rodríguez-Guarado, abstract 221.

therapy exploits that predisposition. If that's true, Powderly said, the incidence of high cholesterol in treated people will plateau, because only predisposed people will suffer hyperlipidemia. The darker possibility is that antiretrovirals will drive up cholesterol in everyone who takes the drugs long enough. D:A:D is far from deciding between those alternatives.

Of course the cardiovascular disease literature already partly addresses Powderly's riddle. People with risk factors like diabetes, obesity, or heart disease in the family stand a bigger chance of winding up with heart problems themselves. Another ICAAC study examined those classic risk factors, along with HIV therapy and its aftermaths, on another lipid marker, triglycerides. Jean-Luc Meynard and coworkers (Saint-Antoine Hospital, Paris) found that PIs raise the risk of skyscraping triglycerides, while NNRTIs lower the risk [abstract 220]. But family history and avoirdupois appeared to weigh more heavily in the triglyceride equation.

Meynard presented a case-control study in which the 76 case patients had at least two triglyceride levels above 4.5 mmol/L or one above 4.5 mmol/L after one above 1.8 mmol/L. The 150 age- and sex-matched controls never saw their triglycerides exceed 1.8 mmol/L. The Saint-Antoine team offered two multivariate models, one based only on clinical records and one based on clinical records plus a self-administered questionnaire. Both analyses controlled for gender, age, the period when a person started HAART, and other variables.

In both models PI experience slightly more than doubled the risk of hypertriglyceridemia, though the *P* values fell short of statistical significance (0.08 and 0.17). Nonnucleoside experience sliced

the high triglyceride risk in both models (odds ratios of 0.29 and 0.16 [*P* = 0.001 for both]). Low CD4⁺ nadirs lowered the odds of hypertriglyceridemia, though not quite significantly, while coinfection with hepatitis C virus sharply reduced the odds (odds ratios of 0.23 [*P* = 0.01] and 0.22 [*P* = 0.1]).

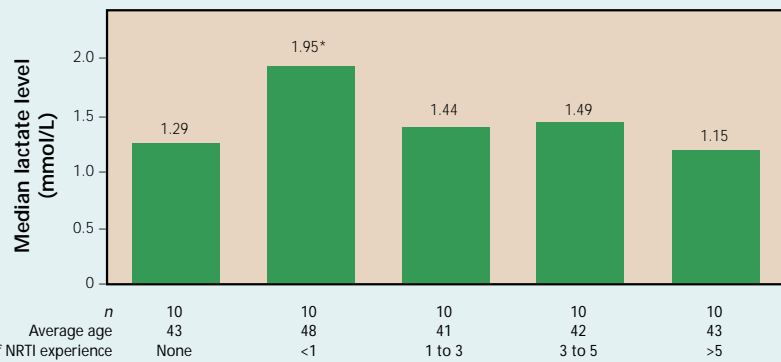
In the model based on clinical records and questionnaires, overweight and family history decidedly raised the risk of elevated triglycerides. A body mass index above 25 kg/m² inflated the risk 2.8 times (*P* = 0.03), and a history of myocardial infarction (MI), stroke, diabetes, high cholesterol, or high blood pressure in a first-degree relative raised the risk 3.65 times (*P* = 0.01).

Meynard and colleagues concluded that, "even if specific risk factors for hypertriglyceridemia are HIV related . . . the more classical risk factors (of which overweight and family history are markers) also play a role."

Another triglyceride study linked high levels to lipodystrophy [abstract 221]. This prospective analysis focused on 95 people who had better than 95 percent adherence to HAART. A. Rodríguez-Guarado and colleagues (Hospital Central de Asturias, Oviedo, Spain) measured their cholesterol and triglycerides every three months and diagnosed lipodystrophy if both clinician and patient agreed on typical signs of the syndrome. Lipodystrophy evolved quickly in some of these good adherers, appearing in 8.8 percent after only six months of therapy. At 18 months 18.8 percent had lipodystrophy, and at 30 months 32.6 percent bore signs of the syndrome.

Before treatment began, cholesterol and triglyceride levels were equivalent in people who ended up with lipodystrophy and in those who didn't. As treatment continued, the lipodystrophy group tended

Figure 1. Does the body compensate for NRTI-induced lactate jumps?



*Significantly higher than the first and last groups ($P < 0.001$).

Source: Marta Boffito, abstract 212.

to have higher cholesterol readings. But after 30 months of follow-up, average cholesterol tallies were high in both groups (211 mg/dL for people without lipodystrophy and 237 mg/dL for people with lipodystrophy, a nonsignificant difference). Triglycerides were consistently higher in the lipodystrophy group from month six to 24 (Table 5), and these levels preceded clinical lipodystrophy in most people who eventually had the syndrome.

One study did try to define the ties between antiretrovirals, classic risk factors, and clinical coronary events, or, more precisely, subclinical events [abstract 1327]. Pascal Chavanet and associates (University Hospital, Dijon, France) picked 99 people who had taken at least triple therapy for at least a year and put them on an exercise bike to probe for signs of silent MI. When the study started no one had coronary artery disease or any cardiovascular symptoms. A standard exercise test spotted silent MIs in 11, a rate equivalent to that of seronegative French people with a high risk of heart disease.

Comparing people with and without silent MIs, the Dijon team found no significant differences in duration of HIV infection or antiretroviral therapy, type of antiretrovirals, AIDS diagnoses, CD4⁺ count, or viral load. Significantly more people with silent MIs had truncal obesity (54 versus 17 percent, $P = 0.004$) and overall obesity (36 versus 8 percent, $P = 0.03$). The silent MI group also had higher glucose levels (5.6 versus 4.88 mmol/L, $P = 0.007$), and they were significantly older (51 versus 42 years, $P = 0.001$). In a multivariate analysis three factors hiked the risk of a silent MI. High total cholesterol

raised the risk 2.2 times; every additional 10 years of age raised the risk 2.6 times; and truncal obesity raised the risk 7.8 times ($P = 0.01$ for all). Chavanet and colleagues published their findings soon after ICAAC.¹⁴

Session cochair William Powderly noted that excess trunk fat signaling lipodystrophy can be tough to tell from simple weight gain in a group this age. Further study with seronegative age-matched controls could clarify the issue, he observed. Another attendee remarked that certain stress tests have higher false-positive rates than others. But Chavanet, who was not the group's exercise physiologist, couldn't say exactly which test was used. Nonetheless, the study fortifies the conclusion that classic risk factors sharply tip the odds toward heart disease in people with HIV infection.

Does the body compensate for high lactate levels?

Two studies added some insight into the prevalence and potential impact of high lactates in people taking NRTIs. In a study of 112 consecutive asymptomatic people with HIV infection, Antonio Antela and colleagues (Ramon y Cajal Hospital, Madrid) recorded a low prevalence of high lactates—only 9.8 percent had levels over 2 mmol/L, and no one had more than 3 mmol/L [abstract 225]. Although most study participants had taken four or more NRTIs, often for several years, Antela found no links between specific drugs and high lactates. In a multivariate analysis, the only factor tied to hyperlactatemia was older age ($P = 0.03$).

The study also found a link between

high lactates and physician-and-patient-defined lipodystrophy. About one third of the cohort had lipodystrophy, usually lipotrophy. The median lactate reading in people with lipodystrophy measured 1.59 mmol/L, compared with 1.21 mmol/L in people without lipodystrophy ($P < 0.001$). And 78 percent of those with lactates above 2 mmol/L had lipodystrophy. Their risk of lipodystrophy was 2.55 times higher than the risk in people with lactates under 2 mmol/L ($P = 0.008$).

Of course the link between high lactates and lipodystrophy doesn't mean they share a cause—mitochondrial toxicity, for example. Both conditions could just be a marker of longer NRTI experience. Time on treatment correlated with high lactates in Antela's univariate analysis, as did total time on abacavir. Yet, even though 87 people in the group had a median 42 months of d4T experience and 102 had taken AZT for 35 months, on the whole lactate elevations remained uncommon.

Whether the moderate lactate peaks reported by Antela have long-term consequences in people taking NRTIs remains open to question, especially in light of a study by Marta Boffito and coworkers (University of Turin) [abstract 212]. She studied five groups of 10 people with HIV infection, sorting them by duration of NRTI therapy. The first 10 had never taken an NRTI, and the remaining groups had ascending durations of treatment (Figure 1). Then she took blood samples for lactate measures, following strict sampling rules: eight hours of fasting and rest, no tourniquets, immediate icing, and centrifugation within 10 minutes.

Boffito found a significantly higher median lactate level in the 10 people who had taken nucleosides for less than one year than in the nucleoside-naive group (1.95 versus 1.29 mmol/L, $P < 0.001$). But compared with the group that took NRTIs less than one year, the groups with more NRTI experience had lower median lactates (Figure 1). In fact, the difference between the under-one-year group and the more-than-five-year group was statistically significant (1.95 versus 1.15 mmol/L, $P < 0.001$). In the under-one-year group, lactates in 90 percent topped 1.5 mmol/L, whereas only 27.5 percent in the other four groups had lactates that high.

The Turin researchers concluded, as others have surmised, that the body may compensate for NRTI-induced lactate ele-

vations and achieve a new equilibrium. Perhaps, they proposed, the NRTI-induced lactate surge triggers some compensatory metabolic mechanism in most people. They ventured no opinion on the nature of that mechanism. But one factor may mar this analysis: The under-one-year group, those with the highest median lactates, was also older than the other groups (Figure 1). And older age, as Antela's study showed, ups the risk of lactate upswings.

ICAAC didn't revive the debate about whether hyperlactatemia and lipodystrophy are mitochondrial toxicities. If they are, people taking tenofovir have something to smile about. Research by the nucleotide's developer ranked the drug among the least mitotoxic NRTIs [abstract 213]. An assay for mitochondrial DNA (mtDNA) content in liver cells, skeletal muscle cells, and renal proximal tubule epithelial cells showed that tenofovir, like 3TC and abacavir, doesn't hinder mtDNA synthesis. Gilead's Tomas Cihlar reported that these tests found more mtDNA depletion with (in ascending order) AZT, d4T, ddI, and ddC. Tenofovir had little effect on lactate production in liver cells (ranking with 3TC and ahead of AZT and ddC) or in skeletal muscle cells (ranking ahead of 3TC, AZT, and ddC).

Probing for connective tissue between PIs and bone disease

A handful of studies addressed possible links between HIV, protease inhibitors, bone density, and fat. The results favored the preponderant view that bones go bad faster in people with HIV infection than in those without it, but the studies didn't settle whether PIs hasten the process. The bottom line for now, sketched in an FDA clinical trial review, is that people taking PIs haven't broken more bones than the PI naive.

Sotirios Tsiodras and coworkers (Deaconess Medical Center and Harvard Medical School, Boston) used DEXA scans of the spine and hip to measure bone mineral density in 100 men and 26 women with or without PI experience and failed to link protease drugs to thinner bones in a multivariate analysis [abstract 1328]. The study used an extensive questionnaire to chart other potential contributors to osteoporosis.

In a univariate analysis, older age, lower body mass index, lack of exercise, testosterone supplementation, and PI therapy all increased the risk of osteopenia. But duration

of PI therapy, duration of HIV infection, CD4⁺ count, viral load, smoking, and alcoholism didn't raise the risk. When statisticians adjusted the risk calculation for age, gender, body mass index, smoking, and exercise, PI treatment no longer heightened the risk of osteoporosis. Older age, lower weight, lack of exercise, and male gender did favor osteopenia in the multivariate analysis.

Joseph Eron (University of North Carolina, Chapel Hill) challenged the conclusion that PIs aren't linked to low bone mineral density, noting that 110 of 126 study participants (87 percent) had PI experience. He suggested that the talk's title—"Osteoporosis is independent of PI use"—could just as easily have been "Osteoporosis not associated with female gender," earning the researchers first-page coverage in *The New York Times*. The analysis suffers, Eron argued, both from the low number of PI-naïve participants and from the low number of women.

A Spanish study offered circumstantial evidence—but not direct proof—that PIs may contribute to bone thinning. S. Padilla (Hospital de Elche) and colleagues cataloged all cases of osteonecrosis in more than 10,000 people with HIV cared for at 19 Spanish hospitals [abstract 216]. They counted all diagnoses of osteonecrosis—based on clinical presentation and radiographic findings—in people with AIDS from 1993 through 2000, and they estimated cases of osteonecrosis in everyone with HIV infection from 1998 through 2000.

No cases were recorded among people with AIDS in 1990, 1991, or 1992. From 1993 through 1996, four cases of osteonecrosis in AIDS patients translated into an incidence of 1.6 cases per 1,000 person-years, compared with 0.04 per 1,000 person-years in the general population. Padilla documented two cases in 1997, three in 1998, four in 1999, and 10 in 2000, yielding an incidence of 14 per 1,000 person-years among people with AIDS for those four years. The estimated incidence for all HIV-infected people in the region rose from near 0 in 1998, to 0.6 per 1,000 person-years in 1999, and to 1.19 per 1,000 person-years in 2000.

Padilla and colleagues concluded that the incidence of osteonecrosis has risen sharply in HIV-infected people since 1997, when PIs first gained wide use in Spain. But that correlation is less than robust because one quarter of the people

with osteonecrosis had never taken a HAART regimen. Growing awareness of possible bone thinning in people with HIV could also contribute to the higher diagnosis rate in recent years.

The Spanish clinicians found no link between lipodystrophy and osteonecrosis in the 23 people with osteonecrosis, but hypertriglyceridemia did emerge as a risk factor [abstract 218]. Six of these 23 people (26 percent) had never taken PIs, and only two had lipodystrophy. Mean total cholesterol measured 189 mg/dL (range 80 to 310 mg/dL), and mean fasting triglycerides measured 155 mg/dL (range 71 to 356 mg/dL). Five of the 23 people (22 percent) with osteonecrosis had fasting triglycerides above 240 mg/dL.

Twenty of the 23 (87 percent) had at least one classic risk factor for osteonecrosis. Besides high triglycerides, these risks were alcohol abuse in eight (35 percent), corticosteroid use by eight (35 percent), treatment with megestrol acetate in six (26 percent), local trauma in four (17 percent), and hypercoagulability in three (13 percent).

Osteonecrosis worsened in 17 of these 23 people over a median follow-up of 17.4 months, and two of them died. Eight had total hip replacements a median of 36 weeks after diagnosis of osteonecrosis, and seven experienced pain relief and "marked functional improvement." The prostheses had to be removed in one person because of surgical infection.

A cell study by Renu Jain and Glaxo colleagues collected data implicating PIs in bone and fat abnormalities, but different PIs had different impacts on bone and fat cells [abstract 219]. Their results, and those of other investigators, provide at least a hypothetical basis for PI involvement in waning bone density. Furthermore, they argue, the simultaneous stifling of osteogenesis and adipogenesis in human mesenchymal stem cells "suggests a causal link between bone and fat formation."

Exposing human stem cells to varying doses of six PIs, Jain estimated differentiation of osteoblasts (bone-forming cells) and adipocytes by measuring alkaline phosphatase activity, total triglyceride accumulation, and expression of the adipogenic marker diglycerol acetyl transferase. The Glaxo team used neonatal rat calvaria (skulls) to measure osteoclast (bone-absorbing) activity. A broad overview of the results (Table 6) suggests that saquinavir and nelfinavir could cause the most trouble

Table 6. Summary of Glaxo's *ex vivo* bone and fat cell experiments

	Stimulated bone resorption (loss of tissue)	Inhibited calcium accumulation	Inhibited osteogenesis	Inhibited adipogenesis	Stimulated release of free fatty acids
Saquinavir	Yes	Yes	Yes	Yes	Yes
Ritonavir	Yes	No	No	No	No
Indinavir	Yes	No	No	No	No
Nelfinavir	Yes	Yes	Yes	Yes	Yes
Amprenavir	No	No	No	No	No
Lopinavir	No	Yes	Yes	Yes	No

Source: Renu Jain, abstract 219.

with bone and fat cells, while indinavir and ritonavir may cause less, and amprenavir the least.

Jain's study is a valuable reminder that protease inhibitors, despite their many shared traits, may have as many differences. Studies in healthy humans confirm, for example, that ritonavir promptly hoists lipids,¹⁵ while indinavir does not.¹⁶ But it's always hard to say how—or whether—cell study results will play out when people with HIV take a certain drug, along with other drugs, against the backdrop of their unique genetic heritage, dietary habits, access to care, and on and on.

If one looks specifically at bone data, cell and mouse studies presented last year showed that indinavir inhibited differentiation of bone-forming osteoblasts,¹⁷ reflecting Jain's findings. Yet in people with HIV taking indinavir, David Nolan and colleagues linked indinavir with *increasing* bone density,¹⁸ despite Jain's cell-study finding that indinavir speeds bone resorption. Another study in humans did lend credence to Jain's amprenavir data (Table 6), finding increasing bone density in 11 people taking amprenavir (with abacavir and 3TC) for 48 weeks.¹⁹ Four studies presented late in 2001 divined no link between PIs and osteopenia.²⁰⁻²³ But one of them found more osteopenia in people taking antiretrovirals than in untreated HIV-infected people,²⁰ and another saw a correlation between *osteoporosis* (but not osteopenia) and PIs.²¹

So this story is far from its denouement. William Powderly's survey of the topic at ICAAC [abstract 1321] itemized precisely what we don't know:

- Is osteopenia linked to protease inhibitors or to antiretrovirals in general?
- Is bone loss progressive, or is the damage limited to a single insult?
- Is this bone loss clinically relevant?

A clinical trial overview by the FDA's Kimberly Struble offered partial answers to questions one and three [abstract 1329]. Her findings exonerated PIs as a specific cause of one highly relevant clinical outcome, fractures. But Struble stressed that her analysis is limited by the typically short duration of clinical trials. Longer treatment, she said, may affect fracture rates, as may briefer treatment with a tactic she didn't evaluate: double PIs.

Comparing first fracture rates in 5,565 people randomized to PI regimens and 4,601 assigned to non-PI therapy, Struble recorded a lower fracture rate with PIs (1.7 percent) than without PIs (2.3 percent). But that difference was not significant, and the non-PI groups may have had a slight disadvantage: 33 percent had taken corticosteroids, compared with 22 percent in PI groups. Still, neither corticosteroids, alcohol, nor tobacco raised the fracture risk in this analysis. The trials didn't collect hormonal or metabolic data that may have influenced bone density.

The fracture incidence in this analysis came to 202 per 10,000 person-years, a rate similar to those in seronegative cohorts reviewed by Struble.

Liver complications loom

Counting broken bones, cases of osteoporosis, or even heart attacks in people taking antiretrovirals may ultimately prove unrevealing, as the drugs improve, people swap therapies, and exposure varies because of treatment deferral and pulsed therapy. But one epidemic of comorbid disease looms large already and could get worse, William Powderly noted in this overview lecture: liver disease. "I believe [liver disease] is going to become a major concern as we move forward with chronic antiretroviral therapy," he said.

A poster report [abstract 241] published around the time of the meeting²⁴ supports

Powderly's concern. Amy Kilbourne (VA Pittsburgh Healthcare System) and coworkers cataloged 19 HIV-related conditions and 13 general medical comorbidities in 811 members of the Veterans With HIV/AIDS Cohort Study, all of whom enrolled in the cohort between June 1999 and July 2000. Far and away the most common comorbidity of either type was hepatitis, in 53 percent. The next most common was also a non-HIV condition, hypertension in 24 percent, followed by an entry in the HIV column (thrush in 21 percent) then by another general condition with cardiovascular consequences (hyperlipidemia in 17 percent).

Of course most of these people—99 percent of them men—didn't get hepatitis because antiretrovirals battered their livers. But coinfection with HIV and a hepatitis virus certainly complicates the treatment of both. Besides coinfection, Powderly noted, many with HIV infection risk liver toxicity as an antiretroviral side effect or as a result of alcohol abuse. In a recent retrospective review of 9,003 people enrolled in AIDS Clinical Trials Group studies, he said, about 10 percent had grade 3 or 4 hepatotoxicity regardless of antiretroviral regimen.²⁵

In some countries with broad access to antiretrovirals, including Italy and Spain, coinfection with HIV and a hepatitis virus is common because injecting drug use accounts for so much HIV infection. A prospective study of 1,283 coinfecting people in Italy documented tardy immunologic recoveries among those starting HAART [abstract 205]. And a Spanish study of 66 coinfecting people with cirrhosis found that HAART didn't improve survival if begun after the onset of cirrhosis [abstract 204].

Gains and losses in new switch and start studies

Concern over treatment toxicities, and hopes that newer drugs will be safer, have prompted what may be the most benign antiretroviral tactic of recent vintage, the preemptive switch. At last October's European Conference, two studies that randomized people to continue a PI or change to efavirenz found efavirenz both more tolerable and more potent virologically—perhaps precisely because it was more tolerable—than continued PI treatment.²⁶

But proactive switching works best in people taking their first regimen and enjoying sub-50-copy RNA suppression.

Table 7. **52-week endpoints after switches to abacavir or efavirenz versus continued PIs***

	Switch to abacavir	P	Switch to efavirenz	P	Continue PI
Reached a virologic or toxicity endpoint (%)	35	0.38 vs PI 0.23 vs EFV	30	0.01 vs PI	47
Two RNA >500 copies/mL (%)	11	<0.01 vs PI 0.09 vs EFV	5	0.57 vs PI	3
Dropout due to toxicity (%)	24	<0.04 vs PI	24	<0.01 vs PI	42

*The study randomized 86 to substitute efavirenz and 81 to substitute abacavir for a PI. Researchers then compared switchers to a nonrandomized control group who continued a PI.

Source: Franco Maggiolo, abstract 1916.

Among people with single or double nuke experience before a PI combo, covert resistant virus may undermine later shifts to non-PI therapies.²⁷ Archived mutants appeared to explain a few virologic failures in one trial of a switch from PIs to abacavir. This open-label study randomly assigned 103 people with sub-50 loads to continue their PI and 106 to switch to Trizivir (AZT, 3TC, plus abacavir) [abstract 671]. Christine Katlama (Pitié Salpêtrière Hospital, Paris) reported that 13 percent in the Trizivir arm had double-NRTI experience before their PI and 2 percent tried NRTI monotherapy. Respective percentages in the continued-PI arm were 8 and 7.

In a 48-week intent-to-treat analysis, 75 percent switching to Trizivir and 69 percent sticking with their PI still had a viral load under 50 copies/mL, a non-significant difference. In an as-treated 48-week analysis, 94 percent taking Trizivir and 90 percent in the PI group stayed under 50 copies/mL. But those 48-week results mask the greater virologic failure rate in the Trizivir arm. Five switching to Trizivir had two consecutive viral loads above 400 copies/mL, compared with one in the PI group. A closer look at those five breakthroughs showed that three involved people with earlier single or double nucleoside experience.

The enduring question about switching from PIs is whether the benefit outweighs the risk. In this trial the benefit came as a reversal of high lipids. Fasting cholesterol and triglycerides shed 0.8 and 0.17 mmol/L among people moving to Trizivir while falling 0.4 mmol/L and rising 0.01 mmol/L in the continued-PI group. Although between-group differences in these lipid changes reached statistical significance ($P < 0.001$), one could wonder about the clinical significance of these changes. The

reported shifts are medians, so half the people who switched to Trizivir enjoyed bigger lipid benefits. And half enjoyed even slimmer benefits, or none at all. In the continued-PI arm, the overall cholesterol improvement and the tiny triglyceride change suggest that study participants had reached a lipid plateau when the trial started, or perhaps they benefited from dietary counseling during the trial.

Another PI switch study [abstract 1916] confirmed the breakthrough risk with an abacavir regimen—as well as the enduring virologic benefit of switching to efavirenz.²⁶ This prospective study at three Italian centers randomized 86 PI takers with a viral load under 500 copies/mL for at least six months to switch to efavirenz and 81 to change to abacavir. Franco Maggiolo (General Hospital of Bergamo) and coworkers compared these switchers to 167 controls who continued a PI after notching an undetectable viral load.

After 52 weeks of follow-up, significantly more people with continuous PI therapy reached a study-defined endpoint—either two consecutive viral loads over 500 copies/mL or a toxicity-induced regimen switch (Table 7). Maggiolo found the abacavir and efavirenz regimens equally tolerable, and significantly more tolerable than continued PIs. Most of the toxic dropouts in the abacavir and efavirenz groups came by week 30.

But people who switched to abacavir endured virologic failure significantly more often than those who stayed with a PI regimen (Table 7). Maggiolo didn't report how many in each group had NRTI experience before their PI regimen. The abacavir group did best in lipid readings, losing an average 10 mg/dL in triglycerides and an average 20 mg/dL in cholesterol through 48 weeks. Lipid levels

stayed constant in the efavirenz group, and triglycerides continued to climb in the PI controls by an average of about 30 mg/dL.

Efavirenz also came out ahead in a comparison of first-line once-daily HAART cornerstones, this time in a contest with saquinavir/ritonavir (1600/100 mg daily) [abstract 670]. Because there aren't enough other once-daily drugs to flesh out these regimens, the NRTI complements to efavirenz or saquinavir/ritonavir made it impossible to build a total once-a-day combination. But that goal is not far off.

Julio Montaner (University of British Columbia) and coworkers randomized 81 treatment-naïve people to start saquinavir/ritonavir and 80 to start efavirenz with NRTIs picked by individual investigators. Mean baseline CD4⁺ counts were similar in the two groups (371 cells/mm³ with saquinavir/ritonavir and 338 cells/mm³ with efavirenz), as were starting viral loads (4.77 and 4.74 logs respectively).

In a 24-week intent-to-treat analysis, 81 percent taking efavirenz and 60 percent in the PI group had a viral load under 50 copies/mL ($P = 0.008$). Efavirenz also did better in the 50-copy on-treatment analysis—90 versus 81 percent—but that difference was not statistically significant.

Dropouts defeated the double-PI regimen. Whereas eight people stopped saquinavir/ritonavir because of side effects, only one couldn't endure efavirenz. Seven people assigned to the PIs “withdrew their consent” (because they couldn't stomach the drugs?), compared with three in the efavirenz group. Nausea, diarrhea, and vomiting were the main complaints among people taking saquinavir/ritonavir. Overall, Montaner counted 25 dropouts in the PI arm and 15 in the efavirenz group. Only one in each arm didn't respond virologically.

At the 24-week mark the two groups had similar gains in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. Some researchers, though, are getting worried about the long-term impact of ritonavir boosting on lipid readings. In his ICAAC toxicity overview, William Powderly suggested that ritonavir's immediate inflation of lipids in healthy volunteers¹⁵ may have lipid implications for so-called baby-dose boosts [abstract 1321].

Powderly's concern seems justified by a recent prospective cohort study in which 27 people started 1,200 mg of amprenavir twice daily (plus 3TC and abacavir) and,

after a median 8.1 weeks, switched to amprenavir/ritonavir at a dose of 600/100 mg twice daily.²⁸ Median cholesterol rose from 155 to 191 mg/dL with solo amprenavir, then to 213 mg/dL 40 weeks after people switched to amprenavir/ritonavir. Median triglycerides climbed from 115 mg/dL at baseline, to 145 mg/dL with amprenavir alone, and to 161 mg/dL 40 weeks after the switch to amprenavir/ritonavir.

A novel though demanding switch strategy involves cycling two distinct combinations every three months in hopes of coaxing a better antiviral response, and perhaps of averting or delaying side effects. The SWATCH study randomized 161 treatment-naïve people to begin ddI, d4T, plus efavirenz, to start AZT, 3TC, plus nelfinavir, or to jump between those combos every three months. Charles Boucher (University of Utrecht) reported eight rebounds in the efavirenz group, seven in the nelfinavir group, and none in the switch group after 48 weeks of follow-up ($P < 0.05$). In a missing-data-equal failure analysis, 69 percent in the switch group versus 57.5 percent in the other two groups had viral loads under 400 copies/mL.

But swapping regimens didn't affect lipids much—cholesterol rose significantly in all study arms, and triglycerides rose significantly in the efavirenz and the switch groups ($P < 0.05$ versus baseline for both gains). Although clinicians in this open-label study thought they saw more lipodystrophy emerge in the steady-efavirenz and steady-nelfinavir groups, DEXA scans found significant fat loss in all three groups, and anthropometric measures discerned no differences between groups. Adherence was close to 95 percent in all three arms, but Boucher noted that the close monitoring in this study may not reflect adherence in “real life.” That may be especially true for people asked to change therapies at every equinox and solstice.

Sharper focus on the TI risk-benefit ratio

If switching to a PI-sparing combination is the most benign antiretroviral tactic (in people with well controlled viremia while taking their first regimen), treatment interruptions (TIs) may be the least benign. A few ICAAC reports addressed the risks and potential benefits of drug holidays, none more exhaustively than a 488-person analysis of the CHORUS cohort [abstract 1909]. More than one third of this group

failed to regain control of replication after their TI, and only half both regained control and got close to their pre-TI CD4⁺ count.

James Braun (Liberty Medical, New York) and colleagues parsed the records of people who took at least one treatment break lasting at least 14 days after August 28, 1996, and then restarted treatment. The group's median CD4⁺ count stood at 288 cells/mm³ when the breaks began, and their median viral load at 3.8 logs (about 6,300 copies/mL). The median TI lasted 94.5 days.

Defining virologic success as reaching a viral load below 500 copies/mL after restarting therapy, the CHORUS team found that 62.1 percent attained that goal. Immunologic success meant reaching a CD4⁺ count within 90 percent of the pre-TI baseline, which some may find a liberal standard. A person starting a TI with 210 cells/mm³, for example, would be rated an “immunologic success” even if the postbreak CD4⁺ count stood at 189 cells/mm³. Braun and coworkers determined that 26.5 percent failed to hoist their CD4⁺ counts to within 90 percent of baseline.

And the treatment breaks took their toll. The group suffered 42 new AIDS diagnoses during the TIs, including 17 cases of wasting, 13 of *Candida* esophagitis, and five of *Pneumocystis carinii* pneumonia (PCP). After restarting treatment, seven people died. The cumulative rate of new AIDS diagnoses or death came to 10 percent. Braun and colleagues added that “the incidence of death and new AIDS-defining events may be underestimated in this analysis” because they limited the study to people who resumed treatment.

Then the CHORUS researchers looked more closely at 130 break takers who stopped their drugs with a viral load below 500 copies/mL (the “suppressed population”) and 326 who stopped with a higher viral load (the “failing population”). Exactly 90 percent of the suppressed group managed to drive their RNA back under 500 copies/mL when they resumed therapy. But a less reassuring proportion, 76.7 percent, came within 90 percent of their pre-TI CD4⁺ count after restarting. The 326 people who quit a failing regimen did worse. Only 51 percent brought their viral load under 500 copies/mL with a new antiretroviral array, and only 72 percent got their count back to 90 percent of baseline after restarting treatment.

Two factors independently predicted

RNA and CD4 success in this cohort. For people with viral loads under 20,000 copies/mL when starting a TI, shorter breaks (10.1 versus 28.1 weeks) favored success. For people with higher viral loads when they stopped antiretrovirals, those on the lower end of “high” (4.18 versus 4.73 logs) had a better shot at success.

When a group of German clinicians sized up TIs with a sterner measure of success—how many starting with an RNA under 50 copies/mL recaptured that golden quotient—they found a substantially lower virologic success rate than the CHORUS team. Eva Wolf (KIS-Curatorium for Immunodeficiency, Munich) and colleagues tracked 127 TI takers for 18 months and matched them with 252 people who didn't interrupt their antiretrovirals [abstract 1910]. Sixty in the TI group suspended treatment with fewer than 50 RNA copies/mL, and 111 noninterrupters started follow-up with sub-50 viral loads. The TIs lasted from two to 12 weeks.

At follow-up month six, 90 percent of the noninterrupters and 77 percent of the break takers still had viral loads under 50 copies/mL ($P < 0.04$). After 18 months of follow-up, 81 percent of the non-TI controls still had viral loads under 50 copies/mL, compared with 63 percent in the TI group ($P = 0.08$). The CD4⁺ trend in the TI takers who started with sub-50 viral loads was equally disheartening. While the sub-50 noninterrupters gained an average 125 cell/mm³ over 18 months of follow-up, the average CD4⁺ count among interrupters changed not a whisker.

Since the TI group started with an average 468 cells/mm³, their failure to gain CD4⁺ cells had little immediate clinical impact. The incidence of new AIDS diagnoses measured 2 events per 100 person-years in the TI group, versus 1 event per 100 person-years in the steady-treatment group, a nonsignificant difference. But that difference may widen with continued follow-up, since substantially more break takers lost control of viral replication. One hint of trouble came in the rates of regimen changes in the sub-50-copy groups—48 percent for those who took TIs versus 28 percent for those who didn't ($P = 0.007$).

In the group as a whole, treatment breaks did confer one advantage: significantly improved lipid and liver readings. Total cholesterol (-50 mg/dL), triglycerides (-225 mg/dL), and aspartate aminotransferase (-40 U/L) all fell significantly after one

month off drugs ($P < 0.0001$ for all), and alanine aminotransferase fell 20 U/L ($P = 0.06$). But Wolf and coworkers didn't report where these lab values stood after 18 months of follow-up.

A big, nonrandomized study like this can etch the contours of TI responses in a typical clinic population, but it leaves lots of details in the shadow. Only one third in the TI group took what Wolf labeled a structured break, while a slightly larger proportion took time off because of toxicity, another 21 percent stopped just because they wanted to, and 5 percent had to shelve their antiretrovirals while fighting off other infections. The analysis is further complicated because 40 in the TI group took a second break, and 11 took a third break. And some of the controls joined the TI ranks as follow-up proceeded. Given these vagaries, Wolf and colleagues did well to suggest the pith of their findings in the poster's last sentence: "The improvement in metabolic parameters [in the TI group] should be carefully weighed against the absence of a CD4⁺ increase."

In a review lecture Steven Deeks (University of California, San Francisco) revisited his experience with people who stop treatment while taking a virologically failing regimen [abstract 422], a group analyzed earlier in print.²⁹ He argued that, "despite significant risks, [structured treatment interruptions] in some patients with drug-resistant virus may be beneficial." Among the "significant risks," he listed five:

- Rapid increases in plasma viremia
- Increased CD4⁺ T-cell activation
- Accelerated CD4⁺ T-cell turnover
- Decreased peripheral CD4⁺ counts
- Emergence of a virus population with greater capacity to replicate in and deplete thymic tissue

Those churning virions and T cells caused big problems for about a third of the 23 people Deeks studied. Despite careful monitoring (this was a prospective study of planned TIs), Deeks logged one case of PCP, one of thrombocytopenia, one of severe peripheral neuropathy, one manifestation of cytomegaloviral infection 12 weeks after salvage therapy started, two cases of non-Hodgkin's lymphoma (one 12 and one 24 weeks into salvage), and one case of progressive Kaposi's sarcoma in a person who later died. Deeks also learned that one person who dropped out

of the study never resumed treatment and died. All these people with clinical progression had 100 or fewer CD4⁺ cells when their TI started.

Treatment breaks lasted for a median 19 weeks in these 23 people, 19 of whom had a complete shift to PI-susceptible virus, and 17 of whom had a shift to NRTI-susceptible virus. As Deeks noted in his published report, though, pre-TI resistant genotypes persisted in peripheral blood mononuclear cells of five of nine study participants who could be evaluated.²⁹

Eight of the 23 (35 percent) did well after they restarted therapy, fully suppressing replication for 12 months. One factor distinguished these eight from less fortunate members of the group: They all had pre-TI virus susceptible to at least one drug class. Five of eight had never taken a nonnucleoside, and three had virus with less than 10-fold resistance to PIs. Would they have done as well if they'd started a new regimen without the break? That question, asked by an attendee after Deeks' talk, can be answered only in a controlled trial.

Preliminary results of one such trial, GIGHAART, do show a better virologic response in people who took presalvage breaks than in people who started salvage immediately.³⁰ But reversion of resistant virus to wild-type did not seem the key to their success, since 19 of 34 had no reversions at all and another five had reversions involving only one antiretroviral class (see "The meaning of early antiretroviral success" in the February 2002 issue of *IAPAC Monthly*).

A new study of consecutive planned TIs charted mixed results even in people many regard as the prime candidates for treatment breaks—those treated during primary HIV infection. José Miró (University Hospital Clinic, Barcelona) and colleagues are studying people treated within 90 days of the first symptoms of primary infection who go on to sustain a viral load below 20 copies/mL and a CD4⁺ count above 500 cells/mm³ [abstract 1908]. After at least one year of d4T, 3TC, and indinavir, they take four two-month breaks and then—barring setbacks—will stay off therapy for a year.

So far 12 people have finished their first two TIs. Five of them had at least a modest CD4⁺ cell proliferative response to HIV p24 (stimulation index > 3) after the first break, and six had such a response after the second break. Three of these six

responders had no viral rebound or a rebound below 5,000 copies/mL during that break. One person without a CD4⁺ proliferative response had a contained rebound after break number two. Miro appropriately tagged the proliferative responses "low level." They didn't persist after treatment resumed.

Sifting through accumulating STI data in an overview talk, Patrick Yeni (Bichat Hospital, Paris) maintained that there are "insufficient data to recommend STIs in any circumstance" [abstract 665]. While some authorities may recommend clinical STI trials for people treated during primary infection, none (to this reporter's knowledge) has issued a stronger endorsement.

These official pronouncements have dissuaded few who see TIs as at least a respite from the antiretroviral grind, and maybe something grander. The CHORUS cohort [see abstract 1909 above] claimed 5,568 members by July 5, 2001. Of those, 2,021—or 36 percent—had stopped treatment for at least 14 days. Of course some of those breaks were mandated by clinical crises, and some were permanent. But the researchers counted 1,155 who stopped for at least two weeks then started again, representing 21 percent of the cohort. The 448 break takers analyzed in the study were those with lab values before and after the break.

What about the on-off therapy being studied, in a nonrandomized trial, at the National Institute of Allergy and Infectious Diseases (NIAID)?³⁴ In his talk on treatment's side effects, William Powderly proposed that threatening toxicities "should lead to more study of novel strategies like intermittent therapy" [abstract 1321]. But, he added, "I'm not sure" that the one-week-on-one-week-off NIAID tactic "is the best approach over a long period." Pulsed therapy, in which treatment resumes whenever CD4⁺s retreat to a predetermined level, may make more sense, Powderly suggested. But he noted that data supporting this approach don't exist.

At ICAAC's interactive session, Daniel Kuritzkes added his voice to this cautionary chorus. Although he rated the NIAID findings⁴ "provocative," Kuritzkes maintained that only randomized trials can tell "whether that's a useful strategy." He also enunciated a fundamental philosophical concern about TIs.

"What worries me," Kuritzkes said, "is that we worked hard to convey the message

Table 8. Mutation-specific responses to tenofovir when added to an incompletely suppressive regimen

Baseline mutation	Mean 24-week time-weighted average RNA change from baseline		
	Tenofovir (n)	Placebo (n)	P
All patients	-0.59 (168)	-0.03 (84)	<0.0001
No 184V	-0.40 (51)	+0.02 (30)	0.0006
184V	-0.68 (117)	-0.05 (54)	<0.0001
184V and no NAMs	-0.97 (42)	-0.16 (16)	<0.0001
No NAMs	-0.85 (54)	-0.18 (23)	<0.0001
NAMs	-0.47 (114)	+0.03 (61)	<0.0001
NAMS and no 184V	-0.39 (39)	+0.09 (23)	0.0002
NAMS and 184V	-0.51 (75)	-0.01 (38)	<0.0001
65R	+0.12 (5)	0	—
NNRTI mutations	-0.49 (77)	+0.02 (44)	<0.0001
PI mutations	-0.55 (96)	0.00	<0.0001

NAMs = nucleoside analog mutations (41L, 67N, 70R, 210W, 215Y/F, or 219Q).

Source: Michael Miller, abstract 1928.

that you have to be on therapy all the time. Cycling may convey the message that you can be on sometimes and off sometimes.” Maybe some people can, but probably not unless they already have well controlled viremia, and certainly not unless they submit to scrupulous follow-up by a committed clinician. And the controlled clinical trials needed to figure out who those people may be have only begun. In the NIAID study they are all people with hefty CD4⁺ counts and viral loads below 50 copies/mL for at least 32 weeks.

Tenofovir resistance and safety scores

ICAAC had a sprinkling of news on new antiretrovirals, Gilead’s recently licensed nucleotide RT inhibitor tenofovir, the investigational PIs atazanavir and tipranavir, and the fusion inhibitor T-1249.

If held in September 2001 as originally planned, ICAAC would have been a grand preapproval datafest for tenofovir. But because ICAAC got postponed until December 2001, the juiciest tenofovir news came out at the October 2001 FDA review. In February 2002, *IAPAC Monthly* reported findings from the pivotal 24-week placebo-controlled trial in which tenofovir, added to incompletely suppressive therapy, knocked viral loads down by an average 0.6 log. A cell study demonstrating tenofovir’s minimal effects on mitochondrial DNA and lactate production has already been mentioned (see “Does the body

compensate” above). Four other tenofovir studies merit attention.

Michael Miller, Gilead’s resistance maven, offered a genotyping substudy of 274 people enrolled in the 24-week placebo-controlled trial [abstract 1928]. Only 3 percent of those taking tenofovir wound up with the drug’s signature *in vitro* mutation, 65R, which ddI and abacavir also elicit. The five people who had 65R when they started tenofovir had no virologic response after 24 weeks. But people with nearly every other conceivable mix of NRTI, PI, and NNRTI mutations had anywhere from a 0.4-log to a 1-log response (Table 8).

Tenofovir seems particularly adept at stalling 184V mutants, even when accompanied by traditional AZT mutations (at codons 41, 67, 70, 210, 215, or 219), and even more so without those extra mutations. In people with none of the AZT mutants (often called NAMs or TAMs for nucleoside or thymidine analog mutations), the average viral load response measured 0.85 log. In people with one or two NAMs, the average response drooped to 0.6 log. And people with three or more NAMs, including 41L and 210W, had only a 0.23-log response. Those two mutations may be critical to tenofovir activity. When Miller looked at people with three or more NAMs not including 41L or 210W, the average response measured 0.65 log.

This study also showed that mutations emerged more slowly in people who added tenofovir to their regimen than in

people who added placebo. NRTI mutations popped up in 24 percent of the placebo group versus 16 percent taking tenofovir ($P = 0.17$). NNRTI mutations arose in 10 percent on placebo and 5 percent on tenofovir ($P = 0.29$). The treatment arms differed significantly in emergence of PI mutations, which appeared in 8 percent taking placebo and 2 percent taking tenofovir ($P = 0.02$).

A study of 5,000 viral isolates that clinicians sent to Virco for phenotyping found that 88 percent fell within the normal range of susceptibility for tenofovir, which Virco set as a 3-fold change from wild-type control [abstract 1756]. Virco’s Richard Harrigan reported that only 51 of the samples (1 percent) had more than 10-fold resistance to tenofovir. Forty-three of these 51 (84 percent) had multiple NAMs, including 215Y/F, and 18 (35 percent) had the multinucleoside-resistant 69S insertion mutations. Only one isolate with more than 10-fold resistance to tenofovir was susceptible to AZT, but 19 (37 percent) were susceptible to d4T and 27 (51 percent) were susceptible to ddI.

A 96-week follow-up of people enrolled in another placebo-controlled study of tenofovir added to an incompletely suppressive regimen documented durable viral suppression and a low rate of side effects [abstract 1929]. Robert Schooley (University of Colorado, Denver) itemized findings in 189 people originally randomized to placebo or to 75, 150, or 300 mg of tenofovir daily for 24 weeks. From week 24 to week 48, everyone in the placebo group got 300 mg of tenofovir, the licensed dose. Follow-up continued through week 96 in 135 people, all taking 300 mg of tenofovir since week 48.

At week 48 the average viral load dropped 0.40 log in the 75-mg group, 0.58 log in the 150-mg group, and 0.62 log in the 300-mg group. At week 96, 48 weeks after the 75- and 150-mg groups switched to 300 mg, viral loads had fallen an average 0.86 log in the original 75-mg group, 0.65 log in the original 150-mg group, and 0.87 log in the group that took 300 mg for the whole 96 weeks.

At the end of the 24-week blinded phase of the study, nine of 54 people (17 percent) taking 300 mg had a grade 3 or 4 side effect, compared with four of 28 (14 percent) taking placebo. Sixteen (30 percent) in the 300-mg group had a grade 3 or 4 lab abnormality, compared with nine (32

Table 9. **Average lipid changes after 48 weeks of atazanavir or nelfinavir**

	Atazanavir (400 or 600 mg once daily)		Nelfinavir (1,250 mg twice daily)	
	Baseline	Week 48	Baseline	Week 48
Total cholesterol (mg/dL)	168	177	165	206
LDL cholesterol (mg/dL)	101	107	97	120
Triglycerides (mg/dL)	125	134	108	162
"Desirable" total cholesterol* (<200 mg/dL) (%)	81	79	82	49

*As defined by the National Cholesterol Education Program.³¹
Source: Ian Sanne, abstract 667.

percent) in the placebo group. After a median 100 weeks of follow-up, 22 of 54 people (41 percent) who took 300 mg the whole time had a grade 3 or 4 side effect, and 28 (52 percent) had a grade 3 or 4 lab abnormality.

Of course it's impossible to say how many of these problems tenofovir caused, and how many must be laid at the door of other antiretrovirals being taken. The most common side effects, depression and weakness, have innumerable causes. The most frequent lab abnormalities in people who took 300 mg for 100 weeks were elevated triglycerides in 15 percent, elevated creatine kinase in 20 percent, and elevated aspartate aminotransferase (AST) in 11 percent.

The high creatine kinase may raise some anxious eyebrows because that's one signal of the kidney problems that helped scuttle approval of a similar Gilead nucleotide, adefovir, as an antiretroviral. But Schooley reported no grade 2 or higher elevations (2.1 mg/dL or more) in anyone who took tenofovir for a median 100 weeks. Eleven in the 75/300-mg arm, eight in the 150/300-mg arm, and six in the 300/300-mg arm had a grade 1 rise (0.5 to 2.0 mg/dL). Nobody in this study had serious renal problems.

Stephen Becker (Pacific Horizon Medical Group, San Francisco) and colleagues from other sites studied 291 people with a CD4⁺ under 50 cells/mm³ or an AIDS diagnosis within the previous 90 days who added 300 mg of tenofovir to a current regimen or started a new regimen including tenofovir [abstract 1930]. Twenty-seven people (9 percent) left the study before week 48 because of drug toxicity, and 119 (41 percent) had some grade 3 or 4 side effect. More, 177 (61 percent), had a grade 3 or 4 lab abnormality, most often triglycerides above 750 mg/dL (34 percent), creatine kinase above 990

U/L (12 percent), lipase above 280 U/L (11 percent), and amylase above 175 U/L (10 percent). Only three people had a grade 3 creatine kinase elevation (3.1 to 6.0 mg/dL), and none had a grade 4 elevation (above 6.0 mg/dL). Earlier treatment with adefovir didn't increase the chance of nephrotoxicity. Given the advanced stage of HIV infection in the group and the many concomitant antiretroviral and other medications, Becker concluded that the rate of side effects and lab abnormalities didn't exceed expectations.

News on two PIs and a fusion inhibitor

If licensed, atazanavir (BMS-232632) would become the third once-daily antiretroviral and the first once-daily PI. It would also be the first PI that doesn't swiftly bump lipids toward the danger zone. At ICAAC a 48-week open-label trial presented by Ian Sanne (WHC Infectious Diseases Clinical Trials Unit, Johannesburg) showed a significantly better response to atazanavir than to nelfinavir [abstract 667]. And the good lipid numbers held steady.

Sanne and colleagues in Argentina, Switzerland, and Thailand randomized 467 treatment-naive people in a 2:2:1 ratio to take 400 or 600 mg of atazanavir once a day or 1,250 mg of nelfinavir twice daily, along with d4T and 3TC. Median starting CD4⁺ counts were 260 cells/mm³ in the 400-mg arm, 283 cells/mm³ in the 600-mg arm, and 273 cells/mm³ in the nelfinavir arm. In a 48-week last-observation-carried-forward analysis, 64 percent taking 400 mg of atazanavir, 67 percent taking 600 mg, and 53 percent taking nelfinavir had a viral load under 400 copies/mL (*P* < 0.05). In an on-treatment analysis, respective proportions with viral loads under 400 copies/mL were 74 percent,

75 percent, and 60 percent (*P* < 0.05). CD4⁺ counts rose an average of about 240 cells/mm³ in all treatment arms.

Baseline numbers for total cholesterol, LDL cholesterol, and triglycerides were equivalent in the combined atazanavir arms and the nelfinavir arm (Table 9). All values rose considerably more among people taking nelfinavir. After 48 weeks of treatment, Sanne figured, 79 percent taking atazanavir and 49 percent taking nelfinavir had a total cholesterol reading within the "desirable range" defined by the National Cholesterol Education Program, that is, below 200 mg/dL.³¹

Hyperbilirubinemia, the most common side effect of atazanavir, affected 5 percent taking 400 mg and 10 percent taking 600 mg. Among people who took at least one dose of their assigned PI, 2 percent taking 400 mg of atazanavir, 13 percent taking 600 mg, and 4 percent taking nelfinavir dropped out because of drug-related side effects.

Atazanavir's favorable lipid profile appears to hold even when the PI is given with 1,200 mg of saquinavir once daily. This combination yielded a virologic response equivalent to that of saquinavir/ritonavir (400/400 mg twice daily) in people with PI experience [abstract LB-16]. But lipids fell in the atazanavir/saquinavir group and rose in the saquinavir/ritonavir group.

David Haas (Vanderbilt University, Nashville) detailed results of this 24-week randomized study, which involved 82 people with about two years of PI experience and viral loads generally between 13,000 and 32,000 copies/mL. Thirty-two took 400 mg of atazanavir with saquinavir, 27 took 600 mg of atazanavir with saquinavir, and 23 took saquinavir/ritonavir. Drug side effects caused the withdrawal of three (9 percent) from the 400-mg arm, nine (33 percent) from the 600-mg arm, and 10 (43 percent) from the saquinavir/ritonavir arm. Four people taking 400 mg of atazanavir got jaundice, as did five in the 600-mg arm.

In a 24-week on-treatment analysis, the average viral load dropped 1.28 logs in the 400-mg arm, 1.17 logs in the 600-mg arm, and 1.5 logs in the saquinavir/ritonavir arm. The saquinavir/ritonavir group had the highest average CD4⁺ gain, 98 cells/mm³, compared with 55 cells/mm³ for 400 mg of atazanavir plus saquinavir and 67 cells/mm³ for 600 mg of atazanavir plus saquinavir.

In the 400- and 600-mg atazanavir/saquinavir groups, mean total cholesterol fell from 223 to 172 mg/dL and from 177 to 140 mg/dL respectively. In people taking saquinavir/ritonavir, the average rose from 191 to 363 mg/dL. Average triglycerides barely changed in the 400-mg atazanavir group, dropped from 199 to 181 mg/dL in the 600-mg atazanavir group, and rose from 202 to 222 mg/dL in the saquinavir/ritonavir group.

The first trial of tipranavir in people in whom a single PI failed didn't afford an adequate appraisal of this vaunted resistance buster. When Virco tested tipranavir against viral isolates with resistance to multiple PIs, 90 percent proved susceptible to tipranavir.³² But in the trial described at ICAAC, nearly half of the 63 study participants had no PI resistance mutations even though a PI regimen had failed in all of them [abstract LB-15].

Charles Farthing (AIDS Healthcare Foundation, Los Angeles) reported equivalent 16-week average viral load drops of about 1.4 logs in the three study arms: 500 mg of tipranavir plus 100 mg of ritonavir twice daily, 1,250 mg of tipranavir plus 100 mg of ritonavir twice daily, and 400 mg of saquinavir plus 400 mg of ritonavir twice daily. The average CD4⁺ count rose from 280 to 360 cells/mm³ in the 500-mg tipranavir group and from 369 to 419 cells/mm³ in the saquinavir/ritonavir group. Oddly, the average count in the 1,250-mg tipranavir group fell from 296 to 290 cells/mm³.

The 1,250-mg tipranavir/ritonavir group also suffered more gut-wrenching side effects than people in the other two arms, with five complaining of vomiting, seven of nausea, and four of diarrhea. Yet only three of 42 people (7 percent) in the two tipranavir arms quit because of side effects, compared with five of 21 (24 percent) taking saquinavir/ritonavir. Four people taking the 1,250-mg dose had a grade 3 or 4 leap in triglycerides, as did three taking 500 mg of tipranavir, compared with one taking saquinavir/ritonavir. Two people in the 500-mg tipranavir arm had a total cholesterol level two or more times above the upper limit of normal.

Boehringer Ingelheim has stopped studying the 1,250-mg dose, focusing now on 500 mg with 100 or 200 mg of ritonavir and 750 mg with 200 mg of ritonavir.

As the Trimeris fusion inhibitor T-20 makes its way through phase III trials, the

company continues to study a second agent in this family, T-1249. A 14-day monotherapy trial in 63 people with heavy antiretroviral experience linked only one factor to virologic response: higher doses of T-1249 [abstract 669]. After variable antiretroviral washout periods, nearly half of the study participants had mutations involving all three current antiretroviral classes, 83 percent had PI mutations, 73 percent had NRTI mutations, and 59 percent had NNRTI mutations. Trimeris's Diego Miralles reported an average 0.1-log dip in viral load with 6.25 mg of T-1249 daily and a 1.4-log tumble with 50 mg daily. Like T-20, T-1249 must be injected.

Adding, subtracting, and forgetting

ICAAC's postponement from September 2001 until December 2001, for reasons painfully familiar to all, occasioned one small coincidence. Speaking at the opening HIV session, Henry Masur (NIAID, Bethesda) noted that December marked 20 years since the *New England Journal* published three articles describing the syndrome later called AIDS.

Two decades later, researchers continue to describe new HIV medicines that may bolster or supplant those already in use. And they continue to describe strategies aimed at easing those drugs' side effects. Among antiretrovirals in development, atazanavir holds particular allure because it leaves lipids largely untouched when given as first-line therapy, and as a second PI it may lower lipids (see abstract LB-16 in the preceding section). Among PIs and NNRTIs, nevirapine appears to be the only other drug with this trait.

But treatment-naïve people starting atazanavir do suffer the fat changes of lipodystrophy.^{33,34} And only when more data on this PI emerge and FDA advisers weigh these findings can clinicians decide whether atazanavir holds a distinct edge over other drugs in the class. It will be interesting to see, for example, whether dosing the drug with low-dose ritonavir changes its lipid profile.

For now, clinicians often face a sour quandary when trying to balance the life-prolonging heft of antiretrovirals against their ponderous toxicities. Drugs like statins, fibrates, and insulin sensitizers blunt spikey metabolic numbers, but they complicate treatment and don't work for everyone. A prospective study of pravastatin

at 20 mg daily in 17 people with PI-related hyperlipidemia logged significant drops in total cholesterol and LDL cholesterol through 12 weeks [abstract 228]. But in 13 people in whom LDL could be calculated, only six met their LDL goal, reported Michelle Lowe (Grady Health System, Atlanta).

Other trials also charted significant lipid reductions with pravastatin³⁵ or fluvastatin.³⁶ But mixed results in a retrospective study of statins and fibrates given to 100 HIV-infected people at a Houston lipid clinic led clinicians there to conclude that it remains "unclear whether [HIV-related] dyslipidemia can or should be managed by using National Cholesterol Education Program guidelines."³⁷

Whatever the ultimate value of statins, fibrates, glitazones, and other side effect soothers, their availability deepens the dilemma about whether to be an adder or a subtracter—whether to add even more drugs to quell toxicities, or whether to fish for simpler, less toxic antiretroviral combos. The debate over that question came to a head at ICAAC's ultimate HIV roundtable, in a spirited give-and-take between Chelsea and Westminster's Brian Gazzard and Massachusetts General's Steven Grinspoon.

Grinspoon had just completed his interactive case study quiz, chronicling the Job-like tribulations of an actual patient with out-of-whack liver function tests, a history of hepatitis, a weight swing from 140 to 205 pounds and down again, low testosterone, a family history of obesity and type 2 diabetes, stratospheric triglycerides, and a fondness for alcohol. After repeated antiretroviral switches, a gaudy panoply of drugs to control his non-HIV complications, and constant counseling, this 41-year-old wound up taking d4T, 3TC, efavirenz, and nelfinavir plus what Grinspoon called his "metabolic cocktail": atorvastatin, gemfibrozil, metformin, and diet.

It worked. He reined in HIV and brought all his mixed-up metabolics back in line. And there's more good news: The audience of several hundred HIV clinicians did great on Grinspoon's quiz, answering many tough questions correctly. (The bad news is that many attendees flubbed badly on Daniel Kuritzkes' resistance quiz.)

But Brian Gazzard found Grinspoon's case troubling. Could this fellow stomach his four-drug antiretroviral cocktail, his

Table 10. **Why people got PCP in the pre-HAART and the HAART eras**

Reason for getting PCP	Percent of those who got PCP	
	1993 to 1996	1996 to 1999
Not in medical care	41	45
In care, met prophylaxis criteria, got prophylaxis (poor adherence?)	44	34
In care, didn't meet prophylaxis criteria, didn't get prophylaxis	9	6.5
In care, met prophylaxis criteria, didn't get prophylaxis	6	14

Source: CDC study cited by Henry Masur, HIV/AIDS keynote session.

three-drug metabolic cocktail, and his diet? Did he actually feel better?

Yes, Grinspoon replied. And he'll live longer because he side-stepped pancreatitis and maybe liver failure.

But, Gazzard persisted, is it essential to get all his metabolic numbers all the way back to normal, despite the burden and risks of polypharmacy?

Yes, Grinspoon maintained. The greater risk here is not drug toxicity, but death. For someone with triglycerides at 500 mg/dL, instead of this man's 1,233 mg/dL, he "wouldn't pull out all the guns."

The case clearly represents an extreme challenge. Any HIV clinician facing such a patient would be happy to have an endocrinologist of Grinspoon's ilk on call. But clinicians are already dealing, on their own, with all sorts of antiretroviral complications. Sometimes those complications can be more acute than HIV infection itself. Yet sometimes the complications may be so distracting that HIV, and its consequences, get short shrift.

That last point could not have been made more clearly than it was by Henry Masur, who authored one of those 1981 *New England Journal* articles on the sudden advent of strange opportunists.³⁸ One might think that, at this stage of the epidemic in wealthy countries, opportunistic infections (OIs) would be the last thing to worry about. But one would be wrong.

OIs have come along for the wild ride through the HAART era, Masur reported, referencing a CDC study of people who got PCP from 1993 to 1996 or from 1996 to 1999 (Table 10). Most people in pre-HAART days and in the HAART age who got PCP did so because they weren't in medical care. Another large proportion in both groups were in care, met prophylaxis criteria, got prophylaxis, but got PCP anyway, maybe because of bad adherence.

But the most distressing number is the last one in the table's third column: 14

percent who got PCP in the golden age of HAART were in care, met prophylaxis criteria, but never got prophylaxis. That percentage more than doubles the rate of errant failure to prophylax in those dangerous days before 1996. ■

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[Strength in Numbers]



[IAPAC Welcomes New and Renewing Members]

In February 2002, the International Association of Physicians in AIDS Care (IAPAC) welcomed 32 new and renewing dues-paying physician members from three countries. IAPAC thanks the following physicians for their support of the association's mission to improve the quality of care provided to all men, women, and children living with HIV/AIDS.

David Aboulafia, *USA*
Eduard Beck, *Canada*
Joseph Beck, *USA*
Paul Benson, *USA*
Leonard Berkowitz, *USA*
Jeff Collins, *USA*
Judy Delmar, *USA*
Harvey Elder, *USA*
Joan Goldberg, *USA*

Frank Graziano, *USA*
Frank Gutierrez, *USA*
Debra Gutterman, *USA*
Christopher Echterling, *USA*
J. Erskine, *USA*
Susan Forlenza, *USA*
Joseph Gathe, *USA*
Lisa Kaplowitz, *USA*
Mary Kasten, *USA*
Arthur Link Jr., *USA*
William Mittendorf, *USA*
Arthur Moswin, *USA*
Joseph O'Neill, *USA*
Paul Pegram, *USA*
Kevin Peterson, *USA*
José Prieto, *USA*
Pilar Ramon, *Spain*
Chris Reust, *USA*
Shannon Schrader, *USA*

Jay Sullivan, *USA*
Nathan Thielman, *USA*
Laura Williams, *USA*
Steven Zell, *USA*

In addition, one corporation renewed its IAPAC corporate partners membership in February 2002. As part of its corporate partners contribution, Bristol-Myers Squibb Virology is subsidizing five developing world physician memberships for a year. IAPAC thanks Bristol-Myers Squibb Virology for its support.

To learn more about IAPAC individual and/or corporate partners membership, please contact Joey Atwell, Associate Membership Director, at (312) 795-4941 or jatwell@iapac.org.

[Member News]

Montaner receives Distinguished Researcher Award in HIV



Julio Montaner

VANCOUVER, British Columbia (Canada) —Boehringer Ingelheim awarded Julio Montaner, Director of the British Columbia Centre for Excellence in HIV/AIDS at St. Paul's Hospital, its inaugural Distinguished Researcher Award in HIV, in recognition of his pioneering work. The award includes a monetary prize of 1 million Canadian dollars, or ±US\$625,000.

Montaner, who is a long-time member of the International Association of Physicians in AIDS Care (IAPAC), has announced his intent to use the award money to endow an AIDS research professorship at the University of British Columbia, where is on faculty as Professor of Medicine. In announcing his decision, Montaner said that it is "... only through continued research efforts that we will eventually find a definitive solution to

this overwhelming pandemic."

IAPAC President José M. Zuniga praised the Argentinean researcher for his extensive experience as well as for his courage in questioning "sacred truths" and, thus, advancing meaningful debate in HIV medicine. According to Zuniga, Montaner has been involved in clinical trials of most of the agents used to treat HIV, and he has a unique perspective gained from his work in clinical research with large groups of patients in Vancouver.

"Yet in praising the clinical contributions he has made to the science of HIV medicine," Zuniga explained, "we must not minimize the contributions Professor Montaner has made in reminding us always of the ethical dimensions of the broader clinical equation."



A B S T R A C T S

Journal of the American Medical Association

Relationships Between Authors of Clinical Practice Guidelines and the Pharmaceutical Industry

Context: Increasing contact has been reported between physicians and the pharmaceutical industry, although no data exist in the literature regarding potential financial conflicts of interest for authors of clinical practice guidelines (CPGs). These interactions may be particularly relevant since CPGs are designed to influence the practice of a large number of physicians.

Objective: To quantify the extent and nature of interactions between authors of CPGs and the pharmaceutical industry.

Design, Setting, and Participants: Cross-sectional survey of 192 authors of 44 CPGs endorsed by North American and European societies on common adult diseases published between 1991 and July 1999. One hundred authors (52 percent) provided usable responses representing 37 of 44 different CPGs that we identified.

Main Outcome Measures: Nature and extent of interactions of authors with drug manufacturers; disclosure of relationships in published guidelines; prior discussion among authors regarding relationships; beliefs regarding whether authors' own relationships or those of their colleagues influenced treatment recommendations in guidelines.

Results: Eighty-seven percent of authors had some form of interaction with the pharmaceutical industry. Fifty-eight percent had received financial support to perform research and 38 percent had served as employees or consultants for a pharmaceutical company. On average, CPG authors interacted with 10.5 different companies. Overall, an average of 81 percent (95 percent confidence interval, 70 percent-92 percent) of authors per CPG had interactions. Similarly, all of the CPGs for 7 of the 10 diseases included in our study had at least 1 author who had some interaction. Fifty-nine percent had relationships with companies whose drugs were considered in the guideline they authored, and of these authors, 96 percent had relationships that predated the guideline creation process. Fifty-five percent of respondents indicated that the guideline process with which they were involved had no formal process for declaring these relationships. In published versions of the CPGs, specific declarations regarding the personal financial interactions of individual authors with the pharmaceutical industry were made in only 2 cases. Seven percent thought that their own relationships with the pharmaceutical industry influenced the recommendations and 19 percent thought that their coauthors' recommendations were influenced by their relationships.

Conclusions: Although the response rate for this survey was low, there appears to be considerable interaction between CPG authors and the pharmaceutical industry. Our study highlights the need for appropriate disclosure of financial conflicts of interest

for authors of CPGs and a formal process for discussing these conflicts prior to CPG development.

(*JAMA*. 2002;287:612-617) Allan S. Detsky et al.

Journal of the International Association of Physicians in AIDS Care

Hospitalization in HIV in Chicago

Background: Reduction in HIV-related morbidity and mortality in the highly active antiretroviral therapy (HAART) era has been unevenly distributed in the United States, and its impact on hospitalizations in urban minority populations in the public sector has been poorly characterized.

Methods: We conducted a retrospective analysis of clinical and administrative data sets of an urban public hospital HIV clinic from 1997 and 1998 to identify the correlates of hospitalization early in the HAART era.

Results: 2,647 unduplicated HIV-infected patients were seen in 1997 and 1998 at the CORE Center. There were 31.7 percent women, 71 percent African-Americans and 12 percent Hispanics, and the mean age was 38 years. Men who had sex with men (MSM), injection drug users (IDU), and heterosexuals each made up one third of the population. A majority of the patients had no health insurance, and 27 percent had Medicaid. The median CD4 T cell count was 266 cells/ μ L, and the median viral load was 1,901 copies/ml. Hospitalizations declined significantly from 1997 (1,579) to 1998 (1,160). Admissions were confined to 25 percent of clinic patients, and 16 patients (range 8-15) had eight or more admissions. African-Americans and Hispanics had significantly more and longer hospitalizations than whites, but there was no difference by gender. IDUs had significantly more admissions than non-IDUs (28 percent vs. 21 percent respectively). On multivariate analysis, lower CD4 T cell count and higher viral load predicted risk of admission in all periods. Unexpectedly, hospitalization rates were high in patients in the highest baseline CD4 T cell stratum, >500 cells/ml (45 of 353, 13 percent), and lowest viral load stratum, <500 copies/ml (103 of 675, 15 percent), and rose from 1997 to 1998. HAART (ie, 1 or 2 drug regimens) predicted fewer hospitalizations compared to 1 or 2 drug regimens. In a subset of patients who filled prescriptions on site, HAART increased from 72 percent to 85 percent and 1-2 drug regimens fell from 28 percent to 15 percent from 1997 to 1998. Regular care was associated with more frequent hospitalization and more hospital days per admission than no regular care. Hospitalized patients had significantly higher mortality than patients not hospitalized (12 percent vs. 2 percent respectively).

Conclusion: HIV-related hospitalizations were frequent in the HAART era and decreased over time. Older age, lack of HAART, lower CD4 T cell count, higher viral load, and minority race predicted hospi-

talization, while gender did not. However, patients with extremely favorable CD4 T cell and viral load counts also had higher than expected hospitalization rates. Three quarters of patients had no hospitalizations, and clustering of hospitalizations in a small number of patients may enable targeted programs to reduce recidivism.

(*JIAPAC*. 2002;1:26-33) Renslow Sherer et al.

Journal of Acquired Immune Deficiency Syndromes

Use of Highly Active Antiretroviral Therapy in HIV-Infected Women: Impact of HIV Specialist Care

Objectives: To evaluate factors associated with use of HIV specialist care by women, and to determine whether medical indications for therapy validate lower rates of antiretroviral use in women not using HIV specialty care.

Design: Cross-sectional analysis of the 1998 interview from the HIV Epidemiology Research Study (HERS) cohort.

Methods: Data from 273 HIV-infected women in the HERS were analyzed by multiple logistic regression to calculate predictors of the use of HIV specialist care providers. Variables included study site, age, education, insurance status, income, substance abuse, depression, AIDS diagnosis, CD4⁺ lymphocyte count, and HIV-1 viral load. In addition, medical indications for therapy and medical advice to begin antiretroviral therapy were assessed.

Results: Of 273 women, 222 (81 percent) used HIV specialists and 51 (19 percent) did not. Having health insurance, not being an injection drug user, and being depressed were predictive of using HIV specialist care (all $p \leq .05$). Although medical indications for therapy in the two groups were comparable, the rate of highly active antiretroviral therapy (HAART) use was significantly higher in women using HIV specialist care (27 percent) compared with those not using HIV specialists (7.8 percent). Women using HIV specialists received significantly more advice to begin antiretroviral therapy (ART) in the 6 months prior to the interview compared with those not using specialists (relative risk, 2.4; 95 percent CI = 1.3-4.6).

Conclusions: Having insurance, not being an injection drug user, and being depressed all increased the likelihood of women receiving HIV specialty care, which, in turn, increased the likelihood of receiving recommended therapies. The level of HAART use (23 percent) and any ART use (47 percent) in these HIV-infected women was disturbingly low. Despite comparable medical indications, fewer women obtaining care from other than HIV specialists received HAART. These data indicate substantial gaps in access to HIV specialist care and thereby to currently recommended antiretroviral treatment.

(*JAIDS*. 2002;29:69-75) Lytt I. Gardner et al.



SAY ANYTHING



[T]here is a risk that the contributions soon to be committed in Africa by the new Global Fund to combat AIDS, tuberculosis, and malaria will not even have a serious possibility of achieving their goals.

A World Health Organization (WHO) warning delivered at a four-day conference in Addis Ababa, Ethiopia, meant to address a dramatic shortage on the African continent of health sector staffing due to poor training programs and healthcare worker migration. Conference delegates from 17 African nations concluded that these challenges have made Africa's healthcare facilities "barely able to function for lack of qualified, motivated doctors, nurses, and other health workers." Ebrahim Samba, the WHO's Regional Director for Africa, urged African health ministers to address these challenges in cooperation with other government leaders in their respective countries, professional associations, private sector healthcare providers, donor countries, and institutions.



It's hard to imagine a worse choice to guide the nation's AIDS policy than Tom Coburn, the former Oklahoma congressman who has spent years denouncing homosexuality and fighting HIV-prevention strategies that rely on condoms. From a January 28, 2002, San Francisco Chronicle editorial entitled, "The Wrong Man for the Job." Coburn and Louis Sullivan, who served as US Secretary of Health and Human Services in the early 1980s, were named Co-Chairs of US President George W. Bush's Presidential Advisory Council on HIV/AIDS. AIDS activists around the United States categorically derided Coburn's selection, calling him a hard-line ideologue whose narrow views should disqualify him from any role in designing federal HIV/AIDS policy.

We must do more to prevent and treat this terrible disease, which continues to ravage the lives of millions of people in America and around the world. We are leading the world on AIDS research and doing our part to stem the tide of this global epidemic. We must remain on the offensive in the battle against HIV/AIDS. We have much work yet to do. HHS and this administration will continue our fight to reduce the impact of this epidemic, both at home and abroad.

US Secretary of Health and Human Services (HHS) Tommy G. Thompson in a February 4, 2002, announcement that US President George W. Bush's proposed budget plan for fiscal year 2003 includes a total of US\$12.9 billion to fight HIV/AIDS—an increase of US\$906 million, or 8 percent over the fiscal year 2002 appropriation.

Of the proposed appropriation, US\$2.8 billion would go to the National Institutes of Health (NIH), which represents a 10 percent increase above the current year's funding level; US\$939 million is for the US Centers for Disease Control and Prevention (CDC), with US\$795 million devoted to support HIV prevention programs in the United States and the remaining US\$144 million dedicated to promoting HIV prevention interventions across the globe; US\$1.9 billion would subsidize the Ryan White CARE Act, with about US\$639 million of the funding made available for the AIDS Drug Assistance Program (ADAP).

Thompson said the proposed HHS budget would allocate US\$410 million to address HIV/AIDS among ethnic and racial minorities. This includes US\$105 million to expand treatment and other services at the Substance Abuse and Mental Health Services Administration



Tommy G. Thompson

(SAMHSA); US\$50 million for the Minorities Communities Fund to support infrastructure development, technical assistance, and prevention and treatment strategies and education in affected communities; US\$124 million under the Ryan White CARE Act; and US\$116 for community-based prevention activities at the CDC.

Also allocated in the proposed HHS budget for 2003 is US\$100 million for the Global Fund to Fight AIDS, Tuberculosis & Malaria. (GFATM). The HHS fiscal year 2002 contribution was US\$100 million. Of note, the US Agency for International Development (USAID)—funded through the US Department of State budget and which itself would enjoy a US\$115 million increase in funding for HIV/AIDS programs over the fiscal year 2002 appropriation —also would contribute US\$100 million to the GFATM in fiscal year 2003.