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# IAPAC

MONTHLY



**Heartbreaks and STIs (or, remembering Dolly)**

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**Retro Part 2:  
Heartbreaks and STIs  
(or, remembering Dolly)**

*Mark Mascolini*



The 10th Conference on Retroviruses and Opportunistic Infections chronicled progress toward understanding three portentous sets of potential antiretroviral side effects: cardiovascular disease, abnormal fat changes, and weakened bones.

But on many critical questions, study results pointed in different directions.

The 10th CROI also served up the first full platter of randomized STI studies, and results proved largely (but not entirely) concordant.

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

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**VICE PRESIDENT/CFO** Harry J. Snyder

**INTERNATIONAL ASSOCIATION  
OF PHYSICIANS IN AIDS CARE**  
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**CONTRIBUTING WRITERS** Carrie Scharrer,  
Mark Wagner

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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

## God's love we deliver

*José M. Zuniga*

I was recently asked to speak at a luncheon honoring volunteers from Los Angeles County churches and synagogues who provide meals each day to HIV-infected patients at the University of Southern California (USC) Medical Center. They are a loosely organized association of congregations, operating with no real budget, permanent staff, or even official title. Moved by a call for compassion that they hear in their respective faiths, the individuals in these congregations identified and found a meaningful method by which to address a pressing need.

For all the beauty that it represents, in its simplicity and in the caring it reflects, this collaborative faith-based effort is not unique. In fact, it is one of tens of thousands of faith-based efforts the world over that are making crucial contributions to the effort against HIV/AIDS.

In Africa, for example, few organizations can match faith-based organizations in terms of their ability to reach significant percentages of the population. This makes faith-based organizations invaluable for prevention education, advocacy, and, in certain cases, provision of care and treatment.

As was made clear at the 2001 African Religious Leaders Assembly on Children and HIV/AIDS held in Nairobi, African churches are to be commended for their willingness to put aside doctrinal differences and forge ecumenical efforts to fight the continental AIDS pandemic. This fact was emphasized by Stephen Lewis, UN Secretary-General Kofi Annan's Special Envoy for HIV/AIDS in Africa, during a keynote address in which he stated that "... some of the finest work combating AIDS on the continent is done through religious communities."

The churches and mosques of Uganda

must be given credit for their role in that country's much-heralded drop in prevalence and incidence rates. Faith-based organizations were critical in disseminating throughout the country information about preventing HIV transmission—the ABC ("abstain, be faithful, condomise") mantra was, indeed, promoted by faith-based organizations.

In the United States, The Balm in Gilead, founded in 1989, has been effective in efforts to involve Christian churches in fighting the spread of HIV among the African-American population. This work is highly important because churches are often at the center of African-American communities, where rates of HIV infection are far outpacing that of the population as a whole. Additionally, The Balm in Gilead, through grants from the US Centers for Disease Control and Prevention (CDC) and the Bill and Melinda Gates Foundation, is working in six African countries to help churches and mosques serve as resources for accurate information on HIV prevention.

And, of global significance, organizations such as the World Council of Churches have banded together to advocate increased efforts from governmental and international institutions in the fight against HIV/AIDS. They have called for increased funding for AIDS treatment and prevention, for foreign debt cancellation for the most-affected countries, and for an end to the stigma and discrimination associated with HIV infection.

Despite these and many other examples of the important work that faith-based organizations are advancing, I was aware, as I prepared my remarks for the USC luncheon, that many of my colleagues have mixed feelings about the role of religion in the global fight against HIV/AIDS. Their concerns are largely based on diatribes from the likes of arch-

conservative Jerry Falwell, who asserts that AIDS is "God's punishment" for a society that tolerates homosexuality. They fear that the involvement of churches, many of which are seen to stand for traditional sexual mores, will lead to an emphasis on "abstinence-only" prevention strategies.

The tendency to paint with broad strokes must be avoided.

Take for example the debate in the US Congress over President George W. Bush's proposed international AIDS relief plan. US Rep. Henry Hyde, a Republican who self-identifies as a religious person, has recognized a higher calling to fight HIV/AIDS by the most effective and humanitarian means possible. The AIDS relief legislation that Hyde has introduced, and which the International Association of Physicians in AIDS Care (IAPAC) supports, takes pains to avoid restricting funding to one particular approach (eg, abstinence) or one specific type of organization (eg, faith-based).

The spirit of such thinking should inform our collective efforts. We must stand behind and support all who can effectively combat this burgeoning pandemic. We should acknowledge that often those people—such as the congregations who provide meals each day to men, women, and children with HIV/AIDS at the USC Medical Center—are those who are motivated by faith in a higher power and a belief that that power has called them to serve others, not in the interest of narrowly defined moral precepts, but for ensuring human dignity and the right to a life free of avoidable suffering and death. ■

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

**Retro Part 2:  
Heartbreaks and STIs  
(or, remembering Dolly)**



Mark Mascolini

**D**olly died on the last day of the 10th Conference on Retroviruses and Opportunistic Infections (CROI). Or, rather, Dolly's handlers put Dolly down.

We write, of course, of the first cloned mammal, the lionized sheep of Edinburgh's Roslin Institute. Dolly's vets decided on euthanasia when a lung infection progressed.

Even in death, Dolly stirred controversy. She was still a tender six years of age. Although no one knows the natural life span of sheep ("Nine months and then we eat them," a cloning expert told *The New York Times*<sup>1</sup>), sheep put to pasture can live a dozen years. Dolly's untimely passing offers yet another example of scientific overreach, some murmured. Though researchers have now cloned mice, pigs, cattle, and a cat, *The Times* noted, many attempts fail, and survivors often endure heart, lung, or immune breakdowns. But classically conceived sheep kept in the barn—as Dolly was for security reasons—often get lung infections and die at around Dolly's age. So maybe Dolly's death says nothing about how far science can push without causing problems.

Such ethical dialectics—as remote as they seem from the world of retroviral disease—have in fact come home to roost with the advent of high-voltage antiretroviral regimens, or HAART. Nothing seemed so clear at the 10th CROI, where study after study asked what new maladies HAART has visited upon its users, and how malignant those maladies may be.

*The second part of this report on the 10th CROI considers potential cardiovascular, metabolic, and osteopathic toxicities of antiretrovirals, as well as treatment interruptions. Part I, which appeared in the April 2003 issue of IAPAC Monthly, looked at new antiretrovirals, other treatment strategies, and the 2NN study of nevirapine and efavirenz.*

One can be dismissive about whether such worries even deserve debate in an ethical arena. And, to be sure, these arguments sound unassailable:

i.

The wretched toxicities of cancer chemotherapy do not prevent us from using these drugs to prolong life. Nor should the ("less," implied) wretched toxicities of antiretrovirals.

ii.

We would not even *know* about long-term antiretroviral side effects if everyone with AIDS still died in the short term.

iii.

The links between antiretrovirals and some toxicities remain controversial, or circumstantial, or reversible when offending agents yield to equipotent but less malefic medicines.

iv.

And one could go on.

No, these arguments can't be countered. But here is the problem with ethical digressions: People with deforming or dangerous side effects don't care about ethical digressions. If you are a clinician or a person with HIV, you already know this. If you are not, scan an online list like "PI-Treatment List" or "Lipidlist," where people surviving HIV because of anti-HIV drugs rage, rage against those drugs' pernicious byproducts—and worry about what other heartbreaks may lurk down the road.<sup>2</sup>

The problem here is not one of hurt feelings or disappointed hopes (though those are problems), but one of acquiescence to risk. Those risks are three:

- Delaying antiretroviral therapy too long
- Interrupting treatment in a planned way
- Interrupting treatment in an unplanned way

The 10th CROI became the first meeting that served up a full menu of randomized

treatment interruption trials, as well as some good observational studies. Almost without exception—and the exception continues to perplex—treatment breaks caused more problems or did no better than continuous therapy. Yet some new work lends credence to the concept of cycling on and off therapy with guidance from CD4 cell (and possibly RNA) changes. And three short-term studies suggested that immune boosting may pay dividends during treatment breaks [abstracts 60-62\*].

Meanwhile, the 10th edition of this yearly meeting chronicled some progress toward understanding three portentous sets of potential side effects: cardiovascular disease, abnormal fat changes, and weakened bones. On many critical questions—alas—evidence pointed in different directions.

### CARDIOCONTRADICTIONS

The 10th CROI showcased the first multi-cohort study linking myocardial infarction to antiretroviral therapy. Within a week of the meeting's end, scrutiny of a similarly huge cohort discovered no tie between antiretrovirals, heart disease, or stroke.<sup>3</sup> While early results from a third study discerned no evidence that protease inhibitors (PIs) thicken artery walls, a fourth study did. And these were not the only heart studies to butt heads and bring on head scratching.

### HIV, hospital admissions, and vascular disease

Two CROI studies failed to find higher rates of coronary heart disease [abstract 747] or thromboembolism [abstract 914] since the arrival of PIs. The just-mentioned published cohort study<sup>3</sup>—first presented at last year's CROI—confirmed these trends in people with HIV infection.

The biggest of these analyses—the published Veterans Administration (VA) study—tracked 36,766 people with HIV

\*Abstracts—as well as all plenary talks and many posters—are online at <http://www.retroconference.org>.

infection (98 percent of them men and 52 percent black) from January 1993 through June 2001, logging their antiretroviral use and hospital admissions for cardiovascular or cerebrovascular disease, while charting deaths from any cause. This study amply illustrates the life-saving prowess of potent antiretrovirals, mapping a drop in deaths from 21.3 per 100 patient-years in 1995 to 5.0 in 2001.

Those downturns do not solely reflect the benefits of potent combinations, since only 41.6 percent had taken a PI (for a median of 16 months) and only 25.6 percent had taken a nonnucleoside (NNRTI) (for a median of nine months). Overall, 70.2 percent took some kind of antiretroviral therapy for an average 15 months. But HAART clearly deserves lots of the credit for the mortality plunge that began just as these therapies entered wide use.

And continued use of PI or NNRTI combos did not inflate the admission rate for heart disease or stroke. From 1995 through 2001, overall admissions for heart disease or stroke slipped from 1.7 to 0.9 per 100 patient-years. When compared with VA patients taking no antiretrovirals, those taking a PI or an NNRTI for fewer than two years, or for two to four years, had almost identical vascular disease admission rates. Nor did admission rates differ between VA patients taking PI combinations and those taking NNRTI regimens. People taking PIs for more than four years still weren't going to the hospital for heart attacks or strokes more than people who never took an antiretroviral.

All this could change, of course, as the VA population ages, as they take PIs even longer, and as the corrosive effects of uncontrolled lipids take their toll. As the authors note, and as Daniel Kuritzkes and Judith Currier stress in a companion essay,<sup>4</sup> the median length of treatment in these people measured a mere 15 months. Meanwhile, use of lipid-lowering drugs climbed from 61 VA patients in 1990, to 140 in 1995, and to 2,417 in 2001. That upswing reflects trends in the population at large, but, the authors add, "in this study population, patients with a history of treatment for diabetes or hyperlipidemia had a much higher rate of vascular events than those without such a history." And most PIs boost lipids. (Six other factors raised the risk of admission for vascular disease: older age, more advanced HIV disease, an AIDS-defining illness, history

of treatment for cardiovascular disease, preexisting vascular disease, and earlier date of first care for HIV at a VA facility.)

So, this salient study offers short-term relief but perhaps no long-term tonic for worries about cardiovascular side effects. A critical question will be whether admission curves start to splay as the VA team compares longer use of PIs versus non-PI regimens.

In a smaller, all-male HIV cohort from Kaiser Permanente of Northern California, longer follow-up than the VA study did not coax out a rising rate of coronary heart disease or myocardial infarction with lengthening PI use [abstract 747]. Nor did Daniel Klein and colleagues detect a heart-disease difference between men exposed to PIs and those who never took them. But, as in an earlier report on this cohort,<sup>5</sup> men with HIV infection landed in the hospital more for heart disease than did age-matched, presumed-seronegative controls.

Klein's study compared three groups:

- 4,025 HIV-infected men who contributed an average two years of non-PI observation
- 2,860 HIV-infected men who contributed an average 3.7 years of PI observation
- 39,425 presumed HIV-uninfected age-matched controls who contributed an average 5.4 years of observation.

An age-adjusted analysis of hospital admission for any coronary heart disease from January 1996 to December 2002 found a significant difference in event rates for the HIV group (6.6 per 1,000 person-years) versus the non-HIV group (3.3 per 1,000 person years,  $P < 0.0001$ ). But event rates for the PI group (7.1) and the non-PI group (6.0) did not differ significantly. When Klein counted only myocardial infarctions, he also found a significant event-rate divergence between the HIV group (3.8) and the non-HIV group (2.6,  $P = 0.03$ ), but not between the PI group (3.9) and the non-PI group (4.0).

If longer treatment with PIs raises the risk of heart disease admissions, it has yet to do so in Klein's cohort—though the numbers do bounce around some. For coronary heart disease, the rate per 1,000 person-years stood at 2.5 for less than one year of PI therapy, 8.9 for one to three years, 4.6 for three to five years, and 12.1 for five to seven years. Respective rates for myocardial infarction were 1.6, 5.0, 2.4, and 6.3.

Shawn Fultz (VA Pittsburgh Healthcare System) reckoned a higher incidence of thrombosis in men with HIV than in uninfected controls [abstract 914]. Fultz and University of Pittsburgh colleagues proposed that a higher thrombosis rate "may be contributing to an increased risk of cardiovascular events" among people with HIV and "has direct implications for clinical management in the perioperative period and regarding long-distance travel."

In the pre-HAART era (before September 30, 1996), the study compared 15,620 HIV-infected VA patients with 14,854 uninfected controls matched for age, race, site, and year of thrombosis diagnosis. The post-HAART comparison involved 29,303 men with HIV and 29,303 controls. Thrombosis incidence proved 40 percent higher in the HIV group than in the non-HIV before HAART and 31 percent higher after HAART. The higher rate in men with HIV did not change after statisticians controlled their calculations for malignancy, atrial fibrillation, HIV-related opportunistic infections, or use of central venous catheters. Thrombosis significantly raised the risk of death in men with and without HIV.

### What D:A:D didn't tell you

Unlike the VA<sup>3</sup> and Kaiser [abstract 747] studies (preceding section), earlier surveys of the HIV Outpatient Study (HOPS)<sup>6</sup> and French men with HIV infection<sup>7</sup> did link PI use with myocardial infarction (MI). And the French study logged a rise in heart attack incidence with longer PI use. Now the D:A:D study—a conflation of 11 European, Australian, and US cohorts—has confirmed a higher MI rate with more years of HAART, defined as a regimen containing a PI or an NNRTI [abstract 130]. (D:A:D stands for Data Collection on Adverse Events of Anti-HIV Drugs.) Although the overall rate of new MIs remained low (3.5 per 1,000 person-years), the adjusted incidence rose 26 percent for every additional year of HAART ( $P < 0.0001$ ). Yet the study, as analyzed so far, leaves key questions unanswered.

Nina Friis-Møller (Copenhagen HIV Program) spelled out findings from the 23,490-person cohort, which will continue to enroll people with HIV at least through 2005 (<http://www.cphiv.dk/dad>). Two thirds of the cohort had taken a PI (for a median of 2.6 years), and one third had tried a nonnuke. An analysis controlling

for other independent MI risk factors (male gender, previous cardiovascular disease, smoking), charted a surging incidence (per 1,000 person-years) with every added year of combination therapy:

- No antiretroviral exposure: 0.05
- <1 year HAART: 2.2
- 1 to 2 years HAART: 2.9
- 2 to 3 years HAART: 3.7
- 3 to 4 years HAART: 4.3
- >4 years HAART: 5.5

Variables that did not affect MI incidence in this analysis were duration of HIV infection, prior AIDS diagnosis, and CD4 nadir. But analysis of other baseline risk factors, adjusted for each other, singled out the following relative MI risks:

- 2.35 times higher risk with versus without diabetes
- 1.16 times higher risk with each higher mmol/L of total cholesterol
- 0.61 times *lower* risk with versus without lipodystrophy

Friis-Møller declined to speculate on that last, counterintuitive finding. Conventional wisdom holds that the increased girth and visceral fat seen in some people with HIV (more on that later) betokens a higher risk of heart disease. In a cohort of this size, objective fat measures could not be made, so investigators relied on subjective clinician reports of fat accumulation, fat loss, or a mix of both. Later at the Retro meeting, Andrew Carr (St. Vincent's Hospital, Sydney) proffered a tantalizing explanation for the D:A:D finding: Clinicians may have classified many simply lean (read: healthier) people as lipoatrophic. Given the nature of the D:A:D study, it will probably be impossible to figure out whether Carr is right. And, given the controversy over what defines HIV lipodystrophy (see "FRAM Frameshift?" below), that's too bad.

But the curious lipodystrophy finding is not the most perplexing D:A:D datum. So far the researchers have not separated people taking PIs from those taking NNRTIs—obviously a crucial distinction. Since the French study toted more MIs with more PI use—unlike the VA and Kaiser studies—it will help to know if *all* HAARTs have the same cardioconsequences in D:A:D, whether the two thirds majority of PI takers drives the rising MI

incidence, or whether some other explanation emerges.

D:A:D's findings also remain a bit murky because researchers counted "definite," "possible," and "unclassifiable" heart attacks as MIs. The "definites" made up 55 percent of the diagnoses, compared with 25 percent "possibles" and 20 percent "unclassifiables." Statisticians reran the analyses counting only "definite" and "possible" MIs, and they found no difference from the results reported. But they didn't analyze just the "definites."

Why do D:A:D's results differ from those of the VA and Kaiser studies? Two possibilities spring to mind.

*i.*

Two thirds of the D:A:D cohort took a PI for a median of 2.6 years. The overall median antiretroviral duration in the larger VA study stretched to only 15 months, and only 1,000 VA patients (2.7 percent of the cohort) took a PI combination for four years or more. Perhaps, as speculated earlier, the VA follow-up has not lasted long enough to expose a PI-MI nexus.

*ii.*

The VA team did not report baseline risk factors, but D:A:D and Kaiser researchers reported some. And the Kaiser cohort—perhaps reflecting social and dietary norms of northern California—had much better heart risk profiles than the international D:A:D drove. Whereas 21 percent of the Kaiser group had ever smoked, 60 percent of the D:A:D cohort had. Only 5 percent of the Kaiser covey had hyperlipidemia before starting a PI, and 20 percent did after PI therapy. In the D:A:D cohort baseline risks included elevated total cholesterol in 30 percent and high triglycerides in 20 percent. Yet the entire Kaiser cohort consists of men, compared with 76 percent of D:A:D enrollees. Could a healthier life-style in the Kaiser group offset the disadvantage of its all-male constituency?

Two other Retro cohort studies endorsed D:A:D's deduction that PIs swell traffic in coronary care units. But these findings were less compelling than D:A:D's results. In a 2,671-person HIV cohort at Johns Hopkins in Baltimore, rates of cardiovascular disease (MI or angina) and stroke

proved about twice as high as national averages—beginning on January 1, 1996 [abstract 132]. During 7,330 person-years of follow-up, Gregory Lucas figured a heart disease incidence of 5.9 events per 1,000 person-years and a stroke incidence of 5.0. In contrast, a national survey of the US population set expected rates at 2 to 2.5 per 1,000 person-years for heart disease and 3 to 3.5 for stroke. When Lucas looked back at the Hopkins HIV cohort from 1990 to 1995, he found only 2.33 cardiovascular "events" per 1,000 person-years.

A multivariate analysis pinpointed seven variables that independently predicted heart disease or stroke, at the following relative odds:

- Hypertension: 3.18
- Use of stavudine (d4T): 2.51
- Age (per 10-year increase): 1.81
- Use of lamivudine (3TC): 1.75
- Use of a PI: 1.61
- Diabetes: 1.41
- Total cholesterol (per 50 mg/dL increase): 1.40

The interesting tie between heart disease or stroke and the popular nucleosides d4T and 3TC suggests that the PI link—which Lucas called "weak"—may not imply causation. Rather, as Lucas noted, it remains plausible that longer survival with potent antiretrovirals (which often meant a PI, d4T, and 3TC in the years after the January 1, 1996 start date for this analysis) contributes to the higher heart disease risk. He added that the analysis could not be controlled for smoking and lipid levels.

Hopkins researchers also collaborated in a cohort study headed by Uchenna Iloeje of Bristol-Myers Squibb, developer of the apparently lipid-friendly PI atazanavir [abstract 746]. The cohort includes 6,711 adults with HIV infection from 18 sites across the United States. Median follow-up among 5,185 people who took PIs measured 3.1 years, but average PI exposure totaled only 1.8 years. Follow-up of the 1,526-person non-PI group stood at 1.7 years.

Event rates proved low in both groups, but lower among people naive to PIs: for cardiovascular disease, 1.6 percent in the PI group versus 0.5 percent in the non-PI group; for coronary heart disease, 1.3 percent in the PI group versus 0.4 percent in the non-PI group. In a linear regression

model, PI therapy proved a less robust risk indicator than current smoking, older age, pre-existing hyperlipidemia, and other classic risk factors (Table 1). Indeed, in these analyses PI use approached, but did not reach, statistical significance. Those findings bolster the oft-made observation that controlling hypertension, diabetes, and smoking matter much more in such equations than stopping PI therapy.

### Carotid intimal intimations

One step removed from actual “events” like heart attacks lie a favored prognosticator of coronary artery atherosclerosis and frank cardiovascular disease: carotid intima media thickness. Studies in people without HIV confirm a higher heart risk with thicker carotid artery walls. Two careful parsings of this parameter offered different answers about PIs’ effects, probably because of differences in study methods, timing, and populations.

AIDS Clinical Trials Group (ACTG) study 5078 has started comparing matched triads of individuals: Every person who has taken a PI for at least two years (median 4.15 years) is matched with one HIV-infected person who never tried a PI and one control not infected with HIV [abstract 131]. Matching criteria are age, race, gender, blood pressure, smoking status, and menopausal status in women. The trial excludes anyone with coronary artery disease or a history of it, diabetes mellitus, uncontrolled hypertension, or a body mass index above 30 kg/m<sup>2</sup>. As a result, noted Judith Currier (University of California, Los Angeles), findings may not apply to a more diverse HIV population.

So far the study includes 44 triads, four of them female. Follow-up will continue for 96 weeks. Currier came to report only baseline comparisons. PI-taking members of each triad have significantly higher readings of three weighty variables—total cholesterol, triglycerides, and waist-to-hip ratio (Table 2). But four years of PI therapy has not thickened their carotid artery walls more than those of the control groups (Table 2). A multivariate analysis did identify four factors that signal thicker artery walls, and two of them—the lipid variables—are hallmarks of PI therapy.

- High-density lipoprotein cholesterol (HDL-C), +0.01 mm per 10-unit decrement ( $P = 0.045$ )

Table 1. Heart disease risks in a 6,711-person HIV cohort

	Cardiovascular disease*		Coronary heart disease*	
	Hazard ratio	P	Hazard ratio	P
PI use	1.99	0.07	2.13	0.08
Current smoker	1.82	0.01	2.26	0.004
Past smoker	1.58	0.11	2.2	0.01
Age 35-49	2.50	0.02	3.1	0.02
Age 50-64	6.28	<0.0001	9.2	<0.0001
Age 65+	20.38	<0.0001	18.08	0.0001
Hypertension	2.03	0.02	2.43	0.006
Diabetes	3.22	0.03	2.01	0.34
Pre-existing CVD*	28.14	<0.0001	23.47	<0.0001
Pre-existing hyperlipidemia	2.93	<0.0001	2.69	0.0005

\*Cardiovascular disease (CVD) included acute myocardial infarction, angina pectoris, coronary artery disease, coronary angioplasty, coronary artery bypass graft, cerebrovascular accident, transient ischemic attack, and peripheral vascular disease. Coronary heart disease included acute myocardial infarction, angina, coronary artery disease, coronary angioplasty, and coronary artery bypass graft. Source: Uchenna Iloeje, abstract 746.

- Low HDL-C and triglycerides above 300 mg/dL, +0.02 mm ( $P = 0.015$ )
- Age, +0.004 mm per one-year increment ( $P = 0.0008$ )
- Body mass index, +0.006 mm ( $P = 0.016$ )

Currier underlined the linked risk with low HDL-C and high triglycerides, citing that as a common finding in people taking PIs.

A 106-person study at the University of California, San Francisco (UCSF) differed from the ACTG effort in three important ways: It did not compare PI takers with a PI-naive or healthy control group; it tracked changes in 22 people over one year; and it measured carotid intima media thickness at 12 sites instead of one [abstract 139lb]. Conveniently, though, baseline PI exposure mirrored that in the ACTG PI group.

Priscilla Hsue found much thicker carotid walls in her baseline measures, averaging 0.9 mm, far above the 0.69 in the ACTG PI group. The difference may reflect the slightly younger age of the ACTG group (42 versus 44.8 at UCSF), lower triglycerides (192 mg/dL versus 225 mg/dL at UCSF), and a lower proportion of smokers (57 percent never smoked versus 42 percent at UCSF). Also, as noted, the ACTG study excluded people with uncontrolled hypertension, and hypertension turned out to be an independent predictor of carotid thickness in the UCSF study, along with older age, higher low-density lipoprotein cholesterol (LDL-C), and a CD4 nadir below 200 cells/mm<sup>3</sup>. Hsue suggested the last finding implies a

tie between chronic inflammation and coronary artery disease in people with HIV. Yet duration of HIV infection did not predict thicker artery walls in her analysis. Neither did HDL-C, a predictor in the ACTG baseline analysis.

Although these differences between study designs and populations may explain the different baseline intima media findings, one-year follow-up in the UCSF study clearly suggests progressive thickening with continued PI use. Among the 22 people followed for one year, nine had hypertension. The median rate of artery wall thickening measured 0.1 mm per year,

### Lopinavir’s metabolic effects in men without HIV

Full-dose ritonavir boosts lipids within weeks in people without HIV infection.<sup>8</sup> While short-term indinavir doesn’t affect lipids in healthy volunteers, it spawns insulin resistance.<sup>9</sup> What about lopinavir/ritonavir?

Grace Lee (University of California, San Francisco) gave standard-dose lopinavir/ritonavir to 10 seronegative men for four weeks, testing them before and after treatment [abstract 748]. Fasting triglycerides rose significantly (from 0.89 to 1.63 mmol/L,  $P = 0.007$ ), as did free fatty acid (from 0.33 to 0.43 mmol/L,  $P = 0.001$ ). Very low-density lipoprotein cholesterol climbed as well (from 15.1 to 20 mg/dL), but the change stopped just short of statistical significance ( $P = 0.054$ ). Other lipid parameters did not change.

During an oral glucose tolerance test, two-hour glucose rose significantly (from 4.6 to 5.9 mmol/L,  $P = 0.05$ ), along with insulin (from 99.64 to 187.9 pmol/L,  $P = 0.04$ ). Insulin-mediated glucose disposal did not change when tested by euglycemic, hyperinsulinemic clamp.

**Table 2. Baseline differences in a study of carotid intima media thickness**

	<i>PI</i> ≥2 years	<i>PI</i> naive	HIV-seronegative	<i>P</i>
<i>n</i>	44	45	48	
Median age (y)	42	41	42	
Total cholesterol (mg/dL)	219	179	187	0.013
Triglycerides (mg/dL)	192	142	107	<0.001
Waist-to-hip ratio	0.92	0.9	0.89	0.001
Intima media thickness (mm)	0.693	0.708	0.687	NS

NS = not significant.  
Source: Judith Currier, abstract 131.

about twice that measured in four studies of people without HIV infection. All await the chance to compare that finding with one-year data from ACTG.

### FRAM FRAMESHIFT?

At the 5th Conference on Retroviruses, Andrew Carr first cataloged fat abnormalities in people with HIV and called the syndrome lipodystrophy.<sup>10</sup> Now, only five years later, we have an evidence-based definition of this disfiguring affliction. In fact, we have two of them, and they disagree on a paramount point—whether central fat accumulation, or hypertrophy, can be called one of HIV lipodystrophy’s distinguishing traits. A formal case definition, published by Carr and international colleagues soon after the 10th CROI,<sup>11</sup> says yes. The Fat Redistribution and Metabolic Change in HIV Infection (FRAM) Study, presented in three detailed CROI posters, says no. Both studies call fat atrophy a hallmark of the condition.

The FRAM posters offer the first full analysis of findings in randomly selected US men with HIV and a control group of age-matched US men enrolled in a long-term heart disease study, CARDIA. Results on FRAM women and controls are still being analyzed, but another study of lipodystrophy in women with HIV confirmed FRAM’s major finding—that fat loss dominates this syndrome. Indeed, in FRAM fat loss affected men with HIV more than CARDIA controls at both peripheral and central sites.

### Less peripheral and central fat

FRAM made no *a priori* assumptions about what fat changes show up most in people with HIV infection. Instead, the study sized up HIV-infected men and women from 18 centers—by self-report,

physical exam, and imaging—and compared them with CARDIA enrollees. Researchers asked study participants to record whether they had noticed mild, moderate, or severe fat changes—either loss or gain—in *both*:

- |                          |                           |
|--------------------------|---------------------------|
| <i>Peripheral sites:</i> | <i>And central sites:</i> |
| • Cheeks                 | • Waist                   |
| • Face                   | • Abdomen                 |
| • Arms                   | • Neck                    |
| • Legs                   | • Chest                   |
| • Buttocks               | • Upper back              |

Then clinicians rated fat at each site.

Barbara Gripshover (University Hospital of Cleveland) reported the analysis for 427 men with HIV and 153 CARDIA controls [abstract 732]. Although both groups had an average age of 39.6 years, the men with HIV were leaner—with a mean body mass index of 24.9 kg/m<sup>2</sup> versus 27.8 kg/m<sup>2</sup> for controls. So it is important to remember, while looking at FRAM’s findings, that the study’s single-exam design cannot show *when* the men with HIV became slimmer than controls—before they became infected, after infection but before antiretroviral therapy, or after they started antiretroviral therapy. Another point worth remembering is that the analyses have not been adjusted for antiretroviral therapy, and most HIV-infected people in FRAM were taking antiretrovirals.

Comparing the HIV group with CARDIA controls, the FRAM team saw these differences:

1. Men with HIV reported losing peripheral fat while controls reported gaining peripheral fat (*P* < 0.001 for cheeks, face, arms, legs, buttocks).
2. More men with HIV than controls reported fat loss in peripheral sites (*P* < 0.001 for cheeks, face, arms, legs, buttocks).

3. Men with HIV reported less fat gain than controls in some central sites (*P* = 0.008 for neck, *P* = 0.012 for waist, *P* = 0.028 for chest).
4. Fewer men with HIV than controls reported fat gain in some central sites (*P* = 0.001 for neck, *P* = 0.003 for waist, *P* = 0.033 for chest).
5. More men with HIV than controls reported fat loss in most central sites (*P* = 0.009 for chest, *P* = 0.022 for waist, *P* = 0.042 for neck, *P* = 0.049 for upper back).
6. Physical exam showed that men with HIV had less peripheral fat than controls (*P* < 0.001 for cheeks, face, arms, legs, buttocks).
7. Physical exam showed that men with HIV had a higher prevalence of peripheral fat wasting than controls (*P* < 0.001 for cheeks, face, buttocks, *P* = 0.013 for legs, *P* = 0.044 for arms).
8. Physical exam showed that men with HIV had less central fat than controls at most sites (*P* < 0.001 for neck and abdominal subcutaneous fat, *P* = 0.007 for chest, *P* = 0.002 for abdominal shape).
9. Physical exam showed a lower rate of central fat gain in men with HIV than in controls (*P* < 0.001 for neck, chest, abdomen, abdominal fat, upper back).

Central fat gains did not correlate with peripheral fat loss in men with HIV—a finding suggesting that these two fat changes have different causes. But central fat loss was associated with peripheral fat loss in men with HIV (*P* < 0.0001).

A second FRAM analysis compared 158 HIV-infected men with clinical lipodystrophy (by self-report confirmed by physical exam), 249 without lipodystrophy, and 153 age-matched CARDIA controls [abstract 733]. Michael Saag (University of Alabama at Birmingham) reported that the lipodystrophy group had significantly lower body mass index, DEXA-measured limb fat, MRI-measured lower trunk subcutaneous fat, and MRI-measured upper trunk subcutaneous fat than did HIV-infected men without lipodystrophy. At the same time, the HIV group without lipodystrophy had significantly lower averages for body mass index, limb fat, and upper and lower trunk subcutaneous fat than did CARDIA controls. Table 3 details these findings.

Compared with controls, the entire HIV group had about 60 percent as much

**Table 3. FRAM differences\* between HIV-infected men with or without lipoatrophy (LA) versus controls**

Measure	All HIV+ vs controls	HIV+ with LA versus controls	HIV+ without LA versus controls	HIV+ with LA versus HIV+ without LA
Body mass index was:	Lower in HIV+ men than in controls	Lower in HIV+ men with LA than in controls	Lower in HIV+ men without LA than in controls	Lower in HIV+ men with LA than in HIV+ men without LA
Total fat was:	Lower in HIV+ men than in controls	Lower in HIV+ men with LA than in controls	Lower in HIV+ men without LA than in controls	Lower in HIV+ men with LA than in HIV+ men without LA
Leg fat was:	Lower in HIV+ men than in controls	Lower in HIV+ men with LA than in controls	Lower in HIV+ men without LA than in controls	Lower in HIV+ men with LA than in HIV+ men without LA
Arm fat was:	Lower in HIV+ men than in controls	Lower in HIV+ men with LA than in controls		Lower in HIV+ men with LA than in HIV+ men without LA
Chest and upper back fat was:	Lower in HIV+ men than in controls	Lower in HIV+ men with LA than in controls	Lower in HIV+ men without LA than in controls	Lower in HIV+ men with LA than in HIV+ men without LA
Head and neck fat was:		Lower in HIV+ men with LA than in controls		Lower in HIV+ men with LA than in HIV+ men without LA
Abdominal and lower back subcutaneous fat was:	Lower in HIV+ men than in controls	Lower in HIV+ men with LA than in controls	Lower in HIV+ men without LA than in controls	Lower in HIV+ men with LA than in HIV+ men without LA
Visceral adipose tissue was:	Lower in HIV+ men than in controls	Lower in HIV+ men with LA than in controls		

\*The table lists only statistically significant differences.  
Source: Michael Saag, abstract 733.

fat in the abdomen, back, and legs. But the men with HIV had about 80 percent as much fat in the chest, back, and arms. Those findings suggest that heavier men with HIV infection carry most of their weight in the upper trunk and arms, noted FRAM’s principal investigator Carl Grunfeld (University of California, San Francisco).

The FRAM team believes these two reports support three conclusions:

- Men with HIV have a syndrome of subcutaneous lipoatrophy in both peripheral and central sites.
- Lipoatrophy is not linked with visceral fat gains.
- Lipoatrophy and lipohypertrophy should be studied separately.

The third FRAM report involved 418 men with HIV and 151 age-matched CARDIA controls [abstract 734]. Andrew Zolopa (Stanford University) reported that physical exam found buffalo hump in 33 men with HIV (7.9 percent) and in 17 controls (11.3 percent), a nonsignificant difference. But the fat pads were 2.5 times bigger in men with HIV than in controls (9.0 x 8.2 cm versus 5.5 x 5.4 cm,  $P < 0.001$ ). In both groups the FRAM team linked buffalo hump with more MRI-measured visceral adipose tissue, a finding suggesting that buffalo hump may be a marker of visceral fat.

### Women’s lipoatrophy study mirrors men’s

A comparison of 608 HIV-infected women and 217 seronegative women in the Women’s Interagency HIV Study (WIHS) mirrored FRAM’s analysis of men in one critical conclusion: Compared with uninfected women, those with HIV more often have both peripheral lipoatrophy and central lipohypertrophy [abstract 736]. Phyllis Tien (University of California, San Francisco) and WIHS colleagues found that “the simultaneous occurrence of peripheral lipoatrophy and central lipohypertrophy was not common in these women.”

The designs of FRAM and the WIHS study had important similarities—and important differences. Like the FRAM researchers, Tien and coworkers charted both fat gain and fat loss in both peripheral sites (arms, legs, and buttocks) and central sites (waist, chest, and upper back). Unlike FRAM, the WIHS study defined lipoatrophy or lipohypertrophy by self-report confirmed by anthropometry—rather than physical exam. WIHS researchers did not get the more objective DEXA and MRI measures that the FRAM team did. But WIHS has one potential advantage over FRAM: Instead of using a cross-sectional (single-evaluation) design, WIHS had 30 months of follow-up.

Over the course of the study, peripheral lipoatrophy evolved in 30 percent of women with HIV and in 13 percent of uninfected

controls. Those rates translated to a 2.4 times higher risk of peripheral fat loss in the HIV group. Similarly, central lipoatrophy appeared in 23 percent of the HIV group and 13 percent of controls, yielding a 1.9 times higher risk in women with HIV. Central lipohypertrophy developed in similar proportions of both groups (29 percent with HIV and 31 percent without HIV), while peripheral lipohypertrophy affected fewer HIV-infected women (19 percent) than controls (26 percent). Weight and overall body fat were higher at baseline in the women without HIV and increased over time. Among women with HIV, weight and body fat did not increase over time.

The WIHS researchers also looked at 154 HIV-infected women and 53 women without HIV who had two of four possible outcomes during follow-up: peripheral or central lipoatrophy, and peripheral or central lipohypertrophy. While both peripheral and central lipoatrophy evolved in 44 percent of the HIV group, both affected only 23 percent of the non-HIV group. Both peripheral and central lipohypertrophy developed in 34 percent of the HIV group versus 70 percent of the non-HIV group. Only 22 percent of the HIV group had peripheral atrophy and central hypertrophy.

Echoing FRAM results in men, Tien and colleagues concluded that “an HIV-associated lipoatrophy syndrome affecting both peripheral and central sites may

**Table 4. Differences between FRAM and the Case Definition Study**

	FRAM	Case Definition
Goal	To “investigate the prevalence of lipoatrophy and lipohypertrophy” in adults with or without HIV infection [abstract 732]	“To develop an objective, sensitive, specific, and broadly applicable case definition of HIV lipodystrophy” <sup>11</sup>
Design	Cross-sectional comparison of fat changes in adults with HIV infection versus fat changes in age-matched uninfected controls	Cross-sectional comparison of HIV-infected people with “at least one moderate or severe subjective lipodystrophy feature” <sup>11</sup> versus HIV-infected people without such a feature
Population	HIV-infected people from 18 US centers and controls in a US heart disease cohort	Consecutive HIV-infected patients from clinics in nine countries on five continents

predominate in women.” The WIHS team urged that lipoatrophy and lipohypertrophy be assessed separately, and in both peripheral and central sites.

**Who fits the case definition? Your computer has the answer**

The *Lancet* article by the HIV Lipodystrophy Case Definition Study Group marks the distinction between its conclusion and FRAM’s in the very first line of the abstract: “Lipodystrophy (peripheral lipoatrophy, *central fat accumulation*, [emphasis added] and lipomatosis) is a common and disfiguring problem in adults with HIV-1 infection and on antiretrovirals.”<sup>11</sup>

The goals of the Case Definition Study, its design, and its population differ starkly from FRAM’s (Table 4). These differences go a long way toward explaining the divergent results of these two studies. If you give two treasure-hunting teams different maps of different countries with different descriptions of what to look for, you would not expect the teams to bring back the same bullion. But if you are an HIV clinician who has lost faith in finding pots of gold, you do hope to learn whether a person’s expanding waist results from antiretroviral therapy, an immune bounce-back, a rediscovered appetite, advancing age, or something else. Or, as FRAM and WIHS results suggest, have you been so distracted by a few paunches that you’re missing *central atrophy*?

Like FRAM, the Case Definition Study is a sophisticated analysis of dauntingly complex, possibly entwined, but perhaps discrete, parameters. Briefly,<sup>12</sup> Andrew Carr and colleagues took these steps to define lipodystrophy:

1. People with HIV from 32 worldwide sites were invited to participate if they did not have active AIDS.

2. Study participants and their clinicians independently recorded lipoatrophy or diffuse fat accumulation in the face, neck, dorsocervical spine area, arms, breasts, abdomen, buttocks, or legs. They counted the focal fat accumulations called lipomas.
3. Study participants and clinicians independently rated the degree of these fat changes as absent, mild, moderate, or severe.<sup>13</sup>
4. People with at least one clinician-confirmed moderate or severe feature (except isolated abdominal obesity) became case patients. People without any such change became controls. People without a clear diagnosis were not assigned to either group.
5. This exercise yielded 417 cases and 371 controls.
6. Objective variables were compared in a univariate analysis apart from antiretroviral and metabolic therapies.
7. Regression analysis involving a training data set of 265 cases and 239 controls pinpointed significant objective variables.
8. The resulting model was tested against a validation data set of 152 cases and 132 controls.

With 79 percent sensitivity and 80 percent specificity, the final model is not perfect, but the researchers argue the result “is good in view of the high variability in body composition.”<sup>11</sup> The model is also complex; it includes 10 variables (Table 5), some of which most clinicians will not be able to measure without heroic effort. Measuring all variables will be much less problematic for research teams who decide to use the model—and its primary purpose is to provide a standard research tool. But clinicians who want to give the definition a test drive can do so—today—by resorting to

simpler models that exclude pricey body composition studies and rely only on clinical and metabolic variables, or only on clinical data (Table 5). Those models are, perforce, less sensitive and less specific than the high-tech version. But, for anyone with Internet access, they are easy to use because they appear online in simple, plug-in-the-data formats:

[http://www.ti3m.com/hiv/default\\_ld.htm](http://www.ti3m.com/hiv/default_ld.htm)

With any of the three models, the online program adds, subtracts, or multiplies points for each measure entered. A final tally of 0 or more indicates lipodystrophy. A score below 0 means no lipodystrophy.

Now. Here’s the nub of the difference between the Case Definition and FRAM: Each of the two trimmed-down Case Definitions has one variable that makes more central girth a feature of lipodystrophy (waist-to-hip ratio or waist circumference), while the full-feathered model has three such variables (waist-to-hip ratio, visceral-to-subcutaneous adipose tissue ratio, and trunk-to-limb fat ratio). If people with HIV lipodystrophy typically have *central atrophy*, as FRAM’s framers contend, the Case Definitions must be wrong. But if more central than peripheral fat does define HIV lipodystrophy, as the Case Definitions say, FRAM must be wrong. Or is there some way both can be right? (We will not touch the possibility that both may be wrong.)

There may be no way out of this box. Or it may be that the just-proposed dichotomy oversimplifies the data. To wit—abdominal CTs showed not only more visceral fat in Case Definition cases than in controls, but also less *subcutaneous* abdominal fat. In this sense the Case Definition and FRAM agree. Also, two Case Definition variables that imply greater girth in cases than controls—the visceral-to-subcutaneous tissue ratio and trunk-to-limb fat ratio—could reflect mostly loss of peripheral fat rather than buildup of central fat. That would also move the data mounds from these studies closer together rather than farther apart.

At a roundtable dissecting FRAM and the Case Definition, Norma Muurahainen (Serono) and Donald Kotler (St. Luke’s-Roosevelt Hospital Center, New York) proposed a way to figure whether the Case Definition and FRAM data sets can be

**Table 5. Variables in three Case Definition models of lipodystrophy\***

Complete model (79% sensitivity, 80% specificity)	Simplified clinical and metabolic model (73% sensitivity, 71% specificity)	Simplified clinical model (75% sensitivity, 60% specificity)
Gender	Gender	
Age	Age	Age
Duration of HIV infection	Duration of HIV infection	Duration of HIV infection
HIV disease clinical stage	HIV disease clinical stage	HIV disease clinical stage
Waist-to-hip ratio	Waist-to-hip ratio	Waist circumference
Anion gap	Anion gap	Change in CD4 cells from nadir
HDL cholesterol	HDL cholesterol	
Trunk-to-limb fat ratio	Estimated LDL cholesterol	
VAT-to-SAT ratio	Triglycerides	
Percentage leg fat	Lactates	

HDL = high-density lipoprotein; LDL = low-density lipoprotein; SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue.

\*Interactive versions of these models are online at [http://www.ti3m.com/hiv/default\\_ld.htm](http://www.ti3m.com/hiv/default_ld.htm)

Source: Reference 11.

reconciled—or whether they’re utterly unmeshable.<sup>14</sup> The Muurahainen-Kotler algebra works like this:

- FRAM collected most of the data needed to complete the Case Definition equation.
- Plugging FRAM data into that equation will tell if FRAM participants have lipodystrophy according to the Case Definition.
- If they don’t, the data sets are irreconcilable.
- And if the data sets are irreconcilable, FRAM and the Case Definition must be swallowed as disparate answers to the same question, either including or excluding central fat accumulation as a hallmark of lipodystrophy.

At face value it appears that the data sets *are* irreconcilable. And it is awfully hard to figure out why. Try to understand this:

- FRAM found that men with HIV have a syndrome of subcutaneous lipoatrophy in *both* peripheral and central sites. In other words, men (and the WIHS study says women) with HIV typically lose arm and leg *and* central fat.
- The Case Definition Study found that *only* 38 case patients—9 percent of all cases—had only lipoatrophy. Another 23 cases (6 percent) had only diffuse fat accumulation. Everybody else, 85 percent, had both.

Can these cohorts—FRAM and WIHS entirely from the United States and the Case Definition cohort from the United States

and eight other countries—really be so different? If these stubborn opposites cannot be reconciled, perhaps one can at least understand how they came to be so contrary. Key decisions made by both the FRAM and Case Definition teams do help explain their findings:

- *FRAM had fat controls.* The men from the CARDIA control group were bigger than the HIV-infected men in FRAM. Controls averaged a body mass index of 27.8 kg/m<sup>2</sup> compared with 24.9 kg/m<sup>2</sup> in the HIV group. (In the Case Definition Study both HIV lipodystrophy cases—at 24.1 kg/m<sup>2</sup>—and HIV-infected nonlipodystrophy controls—at 23.8 kg/m<sup>2</sup>—looked like the FRAM HIV group.) Although the CARDIA guys are a fair sampling of the US male population, that population is the weightiest in the world. Because FRAM’s HIV group weighed less than the controls, they were almost certain to have less visceral fat. So a straight cross-sectional comparison of the HIV men would not pick out visceral adiposity as a trait distinguishing them from these controls.

FRAM researchers could have matched the HIV and control groups for body mass index. But that may have introduced a bias if the HIV group lost weight as a result of their infection. On the other hand, not matching for body mass index also causes a problem, as Donald Kotler, a FRAM investigator, observed: If “body weights and body fat contents [before HIV infection] were lower in those who were to become HIV-infected than in CARDIA controls, the depletion of [subcutaneous adipose tissue] would be

accentuated and the accumulation of [visceral adipose tissue] would be masked”<sup>15</sup> as lipodystrophy developed.

At the aforementioned roundtable, Case Definition point man Andrew Carr noted a related oddity: CARDIA men had more visceral fat volume than HIV-infected men without apparent lipodystrophy.<sup>14</sup> Yet most of the CARDIA controls—and their (American) clinician evaluators—described their bodies as normal. For most Americans, apparently, biggish bellies are normal. But gay HIV-infected men in FRAM may have had an entirely different, slimmer notion of normal. Such diverging perceptions by study volunteers and clinicians asked to rate fat changes can clearly color outcomes.

- *Most people put on pounds with age.* In countries like those represented in FRAM and the Case Definition Study, most people gain weight as they add years. This sad near-certainty may partly explain why an average lipodystrophy case in the Case Definition Study was 45 years old and an average nonlipodystrophy control 39 ( $P < 0.001$ ). Adding inches around the middle as one ambles toward retirement can make it difficult to discriminate pathologic abdominal hypertrophy from simple fattening in an aging cohort. The Case Definition design tried to minimize this confounder by excluding people in whom “abdominal obesity” was the only apparent sign of lipodystrophy. But (returning to Carr’s theory) if gay men perceive a svelter body as normal, they may see the growing girth of older age as abnormal and consider it pathologic, like lipodystrophy. And gay men made up about two thirds of the Case Definition cohort.

- *The Case Definition rests on a priori assumptions.* This is what FRAM chief Carl Grunfeld argues. By giving study participants and clinicians a checklist that already included central fat buildups, the argument goes, the Case Definition Study stacked the odds in favor of the final model featuring more central than peripheral fat. FRAM, in contrast, did not simply ask people if they gained central fat, but rather if they gained or lost central fat or gained or lost peripheral fat. The Case Definition authors allow that “central adiposity and buffalo hump might not be HIV-specific.”<sup>11</sup> Still, when they reran their calculations after excluding the 6 percent of cases with isolated diffuse fat accumulation, or the 19 percent with predominant fat accumulation,

the final model didn't change.

But enough of this titting-and-tatting; let's be nice. Both the Case Definition Study and FRAM are piquant pieces of research that will—together—improve the understanding of fat changes much more quickly than either study would have done alone.

*i.*

Although the complete case definition makes most sense as a research tool, the simpler versions are a boon to HIV medicine that clinicians should use. The advantage reaped will not be an airtight ability to tell people with HIV “yes, you have it” or “no, you don't”—although many curious people will want to know how they stack up against the Case Definition “cases.” The true clinical gain could be a big step toward more systematic tracking of fat changes. Even if central fat gains turn out to be less common or less important than fat atrophy in people with HIV, simply logging the data needed for the interactive program will sharpen clinicians' sense of how their patients are (or are not) changing.

*ii.*

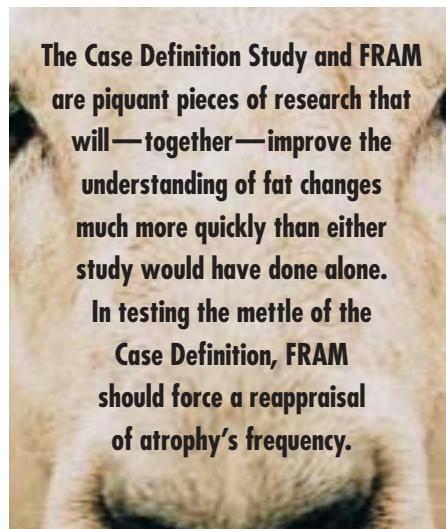
As a research tool the online Case Definition program could have several benefits, as Carr and colleagues observe,<sup>11</sup> including improving assessments of prevalence and incidence from one population to the next, helping define risk factors, giving clues to pathogenesis, and pointing ways to prevention and treatment. If researchers who manage big cohorts pour data into these formulas, much may be learned.

*iii.*

FRAM—whether right, wrong, or just halfway home—deserves credit as an eye-opener. It will force basic scientists, clinical researchers, and clinicians to consider fat atrophy—the HAART era's spectral counterpoint to AIDS wasting—in new ways. What drives it? Does it truly dominate the syndrome? Is it too often overlooked? But most important, in testing the mettle of the standard view of lipodystrophy, as reflected in the Case Definition, FRAM could force faster realization of all those benefits just listed in *ii*.

### Vanishing peripheral fat

If lipoatrophy is as pervasive in people with HIV as FRAM suggests, what makes all that fat go away? Much work lays the blame at the doorstep of the d-drugs, with d4T's doorstep getting particularly cluttered. Five studies show, for example, a sluggish but significant reversal of peripheral fat loss when another nucleoside replaces d4T.<sup>16-20</sup> And two studies at the 10th CROI piled on more evidence implicating this drug. But an interesting new look at the 006 efavirenz trial suggests some big questions remain about nucleosides and subcutaneous fat loss.



With colleagues in Perth, Catherine Cherry (Monash University, Melbourne) used real-time PCR to size up mitochondrial DNA (mtDNA) in 234 samples of subcutaneous trunk or leg fat [abstract 133]. If one buys the hypothesis that mtDNA depletion drives fat loss, the news was not good for the d-drugs—didanosine (ddI), zalcitabine (ddC), and d4T. Samples from people using at least one d-drug had significantly less mtDNA in all tissues studied ( $P < 0.005$ ). The d-drug in the current regimen was the only factor that correlated with less mtDNA in limb fat. Among people taking d4T, subcutaneous limb fat was significantly lower than in people taking zidovudine (AZT) ( $P = 0.001$ ). Ten of 11 people who replaced d4T with AZT or abacavir gained mtDNA in subcutaneous fat. A separate report on these NRTI swappers suggested that replenished mtDNA after the switch from d4T paralleled a reversal of fat cell death [abstract 728].

More evidence linking mtDNA depletion, subcutaneous fat atrophy, and d4T came from a fresh appraisal of 28 people randomized in 1996 to a 72-week regimen including

AZT/3TC or d4T/3TC [abstract 739]. A clinician blinded to each person's treatment diagnosed lipoatrophy in 14 of 17 people (82 percent) assigned to d4T and one of 11 (9 percent) assigned to AZT ( $P < 0.0001$ ). That significant difference held true after adjustment for duration of PI treatment, reported Marc van der Valk (International Antiviral Therapy Evaluation Center, Amsterdam). And results of fat scans and mtDNA tallies buttressed the clinical findings.

The d4T and AZT groups had equivalent mtDNA readings in blood cells frozen before treatment began. Those levels dropped steeply in both treatment arms, but significantly more among people taking d4T (-73 percent) than AZT (-63 percent) ( $P = 0.01$ ). The d4T group also had significantly less central subcutaneous fat by CT ( $P = 0.04$ ), a lower subcutaneous-to-total fat ratio ( $P = 0.005$ ), less peripheral fat by DEXA ( $P = 0.005$ ), and a lower ratio of peripheral to total fat by DEXA ( $P = 0.04$ ). Only two people originally randomized to d4T had switched to AZT, and only one assigned to AZT traded it for d4T. But the results lack absolute rigor because seven people from the original study could not be found, and 10 refused to join the follow-up study.

The seminal 006 face-off between efavirenz and indinavir offered a nice opportunity to compare the effects of regimens containing or excluding nucleosides [abstract 737]. Most will recall that the study randomized treatment-naive people to take AZT/3TC/indinavir, AZT/3TC/efavirenz, or indinavir/efavirenz. Karen Tashima (Miriam Hospital, Providence) used CT scans to chart subcutaneous and visceral fat changes over the course of a year in 89 people taking the nuke-sparing regimen and in 188 taking AZT/3TC with indinavir or efavirenz. The results are illuminating, though imperfect, because people did not have their first scan until about two years after randomization.

Tashima found that 88 percent of sub-study participants had a significant drop in abdominal subcutaneous fat from their first scan to their second regardless of study arm ( $P < 0.05$ ). The nucleoside-sparing group lost a median of 117.5 cm<sup>2</sup> and the nucleoside group 109 cm<sup>2</sup>—a nonsignificant difference. About half of both groups had a significant dwindling of abdominal subcutaneous fat, despite gaining weight. Visceral fat also fell in both groups, but not significantly. Total adipose

tissue dropped by a median of 122.7 cm<sup>2</sup> in the no-nucleoside group ( $P < 0.05$ ) and 101.3 cm<sup>2</sup> in the nucleoside group ( $P < 0.05$ ), and again the between-group difference lacked statistical significance.

Of course this exercise would have been even more revealing if some people took d4T/3TC instead of AZT/3TC. Still, the results have two important implications:

- Abdominal subcutaneous fat can wane significantly in people taking nucleoside-sparing regimens, so nucleosides cannot be blamed entirely for lipoatrophy.
- On average, people can *lose* visceral fat during the third year of antiretroviral therapy, regardless of whether they take nucleosides.

### Facial fat fill-ins and buffalo hump surgery

While switching nukes can slowly reverse depletion of peripheral subcutaneous fat, implants remain the only fix for facial fat atrophy. Two studies of different methods showed good improvement in facial atrophy, although the gain proved transient with autologous fat implants. Three other groups reported varying success and relapse rates with liposuction for buffalo hump.

The ongoing French study of polylactic acid (PLA or New-Fill) injections for facial atrophy showed sustained benefit for up to 96 weeks in 50 people [abstract 719]. Marc-Antoine Valantin (Pitié-Salpêtrière Hospital, Paris) reported that 26 people needed four treatments, 20 needed five, and four people needed only three. The biodegradable synthetic polymer improved ultrasound-measured median cutaneous thickness through week 48 of follow-up, and the gains appeared to hold through week 96:

- Week 6: +5.1 mm
- Week 24: +6.4 mm
- Week 48: +7.2 mm
- Week 72: +7.2 mm
- Week 96: +6.8 mm

Photographs of a few people showed dramatic and sustained improvement through week 96, but reported gains in quality of life at week 48 waned some thereafter. Valantin saw no serious side effects with the procedure, though 22 people (44 percent) had palpable but invisible subcutaneous nodules, which resolved spontaneously in six people.

Autologous fat implants in the face have one advantage over PLA injections—one operation instead of several shots in four or five sessions. But there are disadvantages, too, reported Giovanni Guaraldi (University of Modena) [abstract 722]: The surgery is expensive and requires general anesthesia. Sometimes people with lipoatrophy—37 percent in this 60-person study—don't have enough fat to transplant. The procedure can puff up cheeks too much, an ugly problem that must be corrected by liposuction. Six people needed a “retouch” to correct asymmetry. And the effect can be transient: Ultrasonography recorded a median 5.5-mm gain in subcutaneous fat 24 weeks after surgery and a 3.5-mm gain after 52 weeks.

Ultrasound-guided liposuction yielded good early results for dorsocervical but not submandibular neck fat in a study of 28 people by Jeffrey DeWeese (St. Francis Memorial Hospital, San Francisco) [abstract 721]. Surgeons rated postoperative results excellent for more than a 75 percent drop in fat, good for a 25 to 75 percent drop, and poor for less than a 25 percent drop. They judged dorsocervical results excellent in 21 of those who had liposuction (75 percent), good in five (18 percent), and poor in two (7 percent). Seven people had a recurrence. Among 16 people who had submandibular liposuction, results proved excellent in none, good in 29 percent, and poor in 71 percent. Two people had a recurrence. On a pain scale from 0 to 10, the 23 men and three women averaged 5.3 before surgery, 3.1 two to three months after surgery, and 2.8 more than six months after surgery. Five people had major complications including pancreatitis, anemia, infection, and need for reoperation.

Only one of 18 people endured a recurrence of buffalo hump over eight to 30 months of follow-up in a series reported by Cristina Gervasoni from L. Sacco Hospital in Milan [abstract 723]. Fifteen of these people had liposuction (including the one with a relapse), and three had classical surgical fat removal. Gervasoni saw no surgical complications or local infections. But five of 10 people had a recurrence of buffalo hump after liposuction in a case series reported by Peter Piliero (Albany Medical College) [abstract 724].

The incidence of avascular necrosis is on the rise in a Baltimore cohort, and anti-retroviral-induced lipid changes seem to figure in the surge [abstract 710]. Jeanne Keruly (Johns Hopkins University) uncovered only one case of radiographically confirmed necrosis in 1996 and one in 1997. After that the pace picked up: four in 1998, six in 1999, five in 2000, and 10 in 2001-2002. The rate per 1,000 person-years jumped from 0.81 in 1996, to 2.11 in 1998, to 3.37 in 2001-2002 ( $P = 0.05$  for trend). When Keruly compared these 27 cases with 132 controls matched for cohort entry date and length of follow-up, she discovered 10 factors that separated cases from controls ( $P < 0.05$  for all differences):

- Lipodystrophy (22 percent versus 6 percent)
- Any corticosteroid use (59 percent versus 24 percent)
- Nontestosterone corticosteroid use (37 percent versus 7 percent)
- Higher average CD4 count (357 versus 236 cells/mm<sup>3</sup>)
- Lower average viral load (59,304 versus 179,026 copies/mL)
- Higher average cholesterol (198 versus 159 mg/dL)
- Higher average triglycerides (235 versus 197 mg/dL)
- Use of any protease inhibitor (74 percent versus 45 percent)
- Use of efavirenz (44 percent versus 20 percent)
- Use of d4T (74 percent versus 43 percent)

People with avascular necrosis used PIs or NNRTIs significantly longer than did controls ( $P < 0.05$ ).

The higher lipid readings and higher lipodystrophy rate in the necrosis group suggest a role for altered lipid metabolism. Protease inhibitors can boost lipids, and at least one study linked d4T with hypertriglyceridemia.<sup>21</sup> Keruly observed that corticosteroids may upset lipid metabolism and so cause fatty infiltration of bone marrow. And steroid-induced hyperlipidemia may promote embolization in bone vasculature.

A longitudinal study at the Red Cross Hospital in Athens also traced a link

between bone disease and fat abnormalities, but this time the disease was osteopenia and the fat change was peripheral loss [abstract 764]. The analysis involved 73 men and 13 women, 44 taking a PI regimen and 42 a non-PI combo. People taking anabolic steroids or with a malignancy, chronic diarrhea, or wasting were excluded. George Tsekes used DEXA scans to chart changes in bone mineral density and body fat during about 30 months of treatment.

Body mass index fell significantly (from 24.4 to 23.3 kg/m<sup>2</sup>), as did weight (from 74.5 to 70.9 kg) ( $P < 0.0001$  for both). Total fat loss (19.1 to 15.7 kg,  $P < 0.0001$ ) accounted for the drop in weight; lean tissue did not change. Bone mineral content (from 2,586 to 2,485 g), lumbar spine bone mineral density (from 1.072 to 1.025 g/cm<sup>2</sup>), and  $t$ - and  $z$ -scores also fell significantly in the 30-month span ( $P < 0.0001$  for all). Most of the fat loss came from the arms and legs, although average trunk fat also waned some. Fat loss and bone loss correlated positively ( $r = 0.357$ ,  $P = 0.0007$ ), while bone loss correlated inversely with CD4 gain ( $r = -0.386$ ,  $P = 0.0006$ ). People taking PIs had more bone loss than those taking non-PI regimens, though Tsekes didn't show those numbers. Body fat changes were equivalent in the two treatment groups.

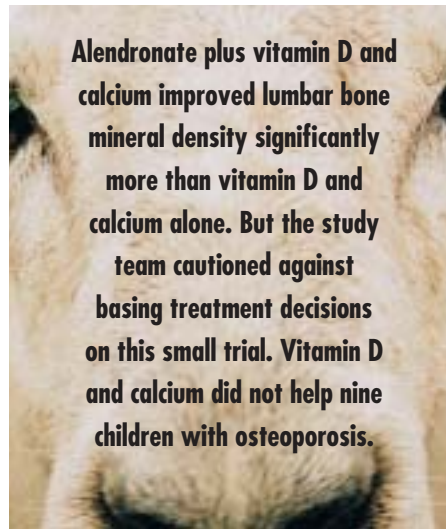
Forty percent of Hispanic and African-American women in a New York study had osteoporosis of the lumbar spine compared with 22 percent of age- and race-matched women without HIV infection [abstract 766]. But Michael Yin and colleagues at Columbia University found no HIV- or antiretroviral-specific risk factors in the HIV group.

Comparing 32 postmenopausal HIV-infected women with 192 HIV-negative controls, Yin found only classic risk factors for osteoporosis: hormone replacement therapy, years since menopause, and low weight before starting antiretrovirals. Nearly half of the women with HIV infection had vitamin D deficiency, but that did not significantly influence risk. Failure to link HIV-specific factors to osteoporosis, Yin proposed, may reflect the small size of the study and a still-poor understanding of risk factors in people with HIV. Still, he recommended vigilance for osteoporosis as the population of US women with HIV grows and ages.

### Alendronate bolsters lumbar density

A 48-week randomized trial comparing alendronate plus vitamin D and calcium with vitamin D and calcium alone recorded significant gains in lumbar bone mineral density in both treatment arms [abstract 134]. But the boost with alendronate (5.2 percent) significantly exceeded the gain in the control arm (1.3 percent).

The study included 31 HIV-infected people—27 of them men and 25 of them white—who had osteopenia reflected in a lumbar spine  $t$ -score below -1 (median -1.52). Those randomized to the alendronate arm took one 70-mg tablet once a week, and everyone took 1,000 mg of calcium and 400 IU of vitamin D daily.



**Alendronate plus vitamin D and calcium improved lumbar bone mineral density significantly more than vitamin D and calcium alone. But the study team cautioned against basing treatment decisions on this small trial. Vitamin D and calcium did not help nine children with osteoporosis.**

All had taken antiretrovirals for at least six months, and most—61 percent—were taking a PI.

Pablo Tebas (Washington University, St. Louis) noted that the lumbar spine improvement rivaled gains seen in people without HIV infection who take alendronate. But he cautioned against basing treatment decisions on results of a small study that included few women and, indeed, many who may not have needed alendronate. Tebas suggested trying lifestyle changes, vitamin D, and calcium for people with osteopenia ( $t$ -score -2.5 to -1) and considering adding alendronate for people with osteoporosis ( $t$ -score  $< -2.5$ ).

Five to 11 months of calcium and vitamin D boosted bone density somewhat—but not significantly—in nine HIV-infected children with osteoporosis studied by Grace McComsey at Rainbow Babies and Children's Hospital in Cleveland [abstract 779]. Comparing 12 children with osteo-

porosis (defined as a  $z$ -score  $< -2$ ) and 11 without osteoporosis, she found a link between longer treatment with NRTIs and PIs and greater bone density.

Nine of the 12 children with osteoporosis took calcium supplements (500 mg once daily if under nine years old and 500 mg twice daily if older) plus 200 IU of vitamin D daily. After five to 11 months of treatment, the median  $z$ -score rose from -2.5 to -1.9, a nonsignificant gain ( $P = 0.08$ ). In untreated children tracked for eight to 21 months,  $z$ -scores hardly changed (median -1.5 to -1.7).

The 12 children without osteoporosis had taken NRTIs for a median of 59 months (range 13 to 130) compared with 35 months (range 0 to 65) in the children with osteoporosis ( $P = 0.008$ ). Median PI treatment duration stretched to 24 months (range 13 to 48) in the children without osteoporosis versus 11 months (range 0 to 45) ( $P = 0.037$ ) in the children with osteoporosis. Children with osteoporosis were somewhat lighter than those without osteoporosis (body mass index 17.6 versus

### Some renal risk with tenofovir?

Kidney problems helped kill adefovir's chance as an antiretroviral. Two reports at the 10th CROI cataloged six cases of similar side effects in people taking the nucleotide that did get an antiretroviral license, tenofovir. Three of the people had tried adefovir earlier, and three had low weight.

Gary Blick (New York Medical College, Valhalla) reported hypophosphatemia in three men three to seven months after they started tenofovir [abstract 718]. All had heavy treatment experience and had taken adefovir. Phosphorus repletion therapy helped, but two of the men had to stop tenofovir and their other antiretrovirals temporarily. Phosphorus levels dropped again when they resumed tenofovir therapy and stopped phosphorus repletion. Blick and colleagues suggested urinalysis and regular monitoring for serum phosphorus, creatine, and CO<sub>2</sub> when giving tenofovir to adefovir veterans.

Jacques Reynes (CHU Montpellier, France) saw two women and one man with low phosphates and the renal tubular defect Fanconi syndrome [abstract 717]. Phosphorus dropped and creatinine climbed eight to 11 months after they started tenofovir. Both levels returned to normal when they stopped the drug, and biologic signs of renal tubular injury resolved. All three weighed less than 60 kg. Noting earlier reports of two similar cases,<sup>22,23</sup> Reynes suggested periodic screening for phosphatemia, glucosuria, proteinuria, and serum creatine in people—especially slim people—taking tenofovir.

20.6 kg/m<sup>2</sup>,  $P = 0.09$ ) and had marginally higher phosphorus levels (4.8 versus 4.5 mg/dL,  $P = 0.08$ ). The groups did not differ significantly in gender, age, or CD4 percent.

## WHY TRY AN STI?

After several years of speculation, anecdote, and small-fry case series, research on structured treatment interruptions (STIs) has matured. One sign of this seasoning is the roster of the 10th CROI's slide session on "treatment strategies." All six strategies were treatment breaks. And all six treatment breaks got tested in randomized trials. Here's the bottom line:

*Treatment breaks make most sense for people who don't need treatment.*

That's close to the conclusion offered in the meeting's last talk by Huldrych Guenthard (University Hospital Zürich), who probed the six prospective studies as well as the Swiss-Spanish Intermittent Treatment Trial (SSITT) that he helped run [abstract 190]. Guenthard proposed four scenarios in which stopping drugs seems reasonable:

- For people with severe drug toxicity
- For people who started treatment during primary infection
- For people who started treatment with a high CD4 count

*And, maybe:*

- For people with high CD4 counts in whom CD4 numbers guide drug breaks

Despite two CROI reports supporting that last rationale, Guenthard called for more study and longer follow-up before this concept becomes canon. STI formats with predefined break periods, as in SSITT, seem riskier than CD4-guided breaks. Guenthard also listed two STI rationales that now sound dubious to him:


- For people with controlled chronic infection who want an immune boost
- For people starting salvage to promote susceptibility to more drugs

Guenthard marshaled SSITT study results to defend his dismissal of immune boosting through "autovaccination" with

one's own virus. Two trials that looked at presalvage STIs—with very different designs, in very different people—reached very different conclusions.

### Triggering breaks with T-cell tallies

Three earlier studies showed that many people who began antiretroviral therapy with CD4 counts or viral loads no longer considered grounds for intervention can safely stop treatment for a year or more.<sup>24-26</sup> CD4 counts fall and viral loads climb, but restarting the same regimen at preset cutoffs almost always gets HIV back under control. In the largest of these studies, a chart review,<sup>24</sup> the best responders were those with the best pretreatment numbers—people who would not start antiretrovirals if their clinicians follow today's guidelines.



**Featuring six randomized trials of structured treatment interruptions, the meeting offered the first rigorous look at this controversial strategy. STIs guided by CD4 counts looked safe in people with high pretreatment T-cell tallies. STIs before salvage looked either ineffective or dangerous.**

The same held true for a 120-person trial that randomized people to continue treatment or to take drug holidays that would end if the CD4 count dipped below 350 cells/mm<sup>3</sup> twice in a row, if the viral load topped 100,000 copies/mL twice in a row, or if they suffered a new AIDS diagnosis or the acute retroviral syndrome [abstract 65].

This open-label study run by Lidia Ruiz (IrsiCaixa Foundation, Barcelona) enrolled people with a treatment-induced viral load below 50 copies/mL, a CD4 count above 500 cells/mm<sup>3</sup>, and a CD4 nadir above 100 cells/mm<sup>3</sup>. In fact, most had much higher nadirs, with medians of 416 cells/mm<sup>3</sup> in the TI group and 379 cells/mm<sup>3</sup> in the continuous treatment group. Only 8 percent of study participants had an AIDS diagnosis on their chart.

The acute retroviral syndrome flared

up in six people (10 percent) when they stopped treatment, and 24 break takers (41 percent) had one or more minor symptoms. Five people saw their CD4 count fall below 350 cells/mm<sup>3</sup> while off therapy and—in a risky move—refused to resume treatment because they "felt well." (The psychological impact of STIs remains understudied.) No one chalked up a new AIDS diagnosis and no one's CD4 count sank below 200 cells/mm<sup>3</sup>. All told, 33 people had to restart HAART because of falling CD4s, rising viral loads, or both. The other 26 people in the STI arm (44 percent) remained off treatment for 48 weeks. In the constant treatment group, CD4 counts remained stable and all but two maintained an undetectable viral load.

Ruiz tracked down five variables that separated the 26 holiday takers who stayed off therapy from the 33 who restarted:

- Higher CD4 nadir: 454 versus 363 cells/mm<sup>3</sup> ( $P = 0.06$ )
- Higher pretreatment CD4 count: 524 versus 318 cells/mm<sup>3</sup> ( $P = 0.0425$ )
- Higher pre-HAART CD4 count: 586 versus 393 cells/mm<sup>3</sup> ( $P = 0.0257$ )
- Lower week 4 viral load: 4.2 versus 5.4 logs ( $P = 0.0003$ )
- Flatter week 4 CD4 slope: -138 versus -264 cells/mm<sup>3</sup> ( $P = 0.09$ )

In a multivariate analysis lower CD4 nadir and higher pretreatment viral load predicted the need to restart therapy.

An ambitious trial by the HIVNAT group in Bangkok compared three strategies: continuous treatment, CD4-guided STIs, and week-on/week-off STIs [abstract 64]. Jintanat Ananworanich and colleagues studied 74 adults (38 of them women) who began treatment with two nucleosides, graduated to two nukes plus a PI, and started this trial while taking two nukes and 1,600 mg of soft-gel saquinavir plus 100 mg of ritonavir once daily. In the CD4-guided arm, a 30 percent drop in T cells or a drop below 350 cells/mm<sup>3</sup> triggered renewed treatment. Baseline CD4 counts ranged from 464 to 872 cells/mm<sup>3</sup>.

The week-on/week-off strategy proved the most prone to failure, but partly because of how HIVNAT defined failure. In the steady treatment and on/off arms, failure meant a viral load above 1,000 copies/mL or a CD4 count below 350

**Table 6. Two STI tactics versus continuous therapy in Thailand**

	<i>Continuous therapy</i>	<i>CD4-guided STI</i>	<i>Week-on/week-off STI</i>
<i>n</i>	25	23	26
Mean wk after randomization	44	46	44
<i>n</i> (%) failures*	0	NA	10 <sup>†</sup> (38)
CD4 >350 cells/mm <sup>3</sup> (%)	100	87 <sup>‡</sup>	96
Viral load <500/50 copies/mL (%)	100/96	100/83 <sup>¶</sup>	54/35 ( <i>P</i> < 0.05 vs other arms)
Median CD4 change (cells/mm <sup>3</sup> )	+5	-178 <sup>‡</sup>	-6
Time on treatment (%)	100	33	59

\*Failure meant a viral load above 1,000 copies/mL or a CD4 count below 350 cells/mm<sup>3</sup>. There were no failure criteria in the CD4-guided arm.

<sup>†</sup>Seven virologic failures, one CD4 failure, two lost to follow-up.

<sup>‡</sup>Twelve people off treatment at this point.

<sup>¶</sup>Includes only 12 people with ≥12 weeks of retreatment.

NA = not applicable.

Source: Jintanat Ananworanich, abstract 64.

cells/mm<sup>3</sup> at any time through week 48. There were no 48-week failure criteria for people in the CD4-guided arm because they stayed off treatment until their counts dropped 30 percent or below 350 cells/mm<sup>3</sup>. As Table 6 shows, no one receiving continuous HAART had a study-defined failure, while the on/off group had 10 failures—one because of a CD4 drop, seven because of a viral load surge, and two because of loss to follow-up.

People randomized to a CD4-guided STI naturally had the biggest T-cell deficit through 48 weeks of study. They also enjoyed the most time off treatment: 67 percent versus 41 percent in the week-on/week-off arm, and by definition 0 percent in the continuous therapy arm. Yet all that time off treatment in the CD4-guided arm yielded no benefit in serum lipids or quality of life. The acute retroviral syndrome felled one person taking a CD4-guided STI.

After a median 72 weeks of follow-up—with failures now possible in the CD4-guided arm—their failure rate equaled that of the continuous treatment arm: 4 percent (one of 23 people versus one of 25 in the continuous arm). At 72 weeks Jintanat counted 12 failures among 26 people (46 percent) in the on/off arm.

### Resistance risk in preset on-off STIs

The iffy outcome with week-on/week-off therapy in the HIVNAT study (preceding section) diverges from results with the same strategy at the US National Institute of Allergy and Infectious Diseases (NIAID).<sup>27</sup>

Mark Dybul has reported that none of eight people who stuck to the week-on/week-off schedule suffered a viral load breakthrough above 500 copies/mL or a 30 percent tumble in T cells after 32 to 68 weeks. Six of the eight had rare blip-like spikes by the end of some weeks off therapy, but none above 261 copies/mL. (Another person who stopped treatment for 10 days instead of seven rebounded to 3,101 copies/mL.)

In a poster [abstract 639] and his plenary talk [abstract 190], Huldrych Guenthard also noted speedy though spare rebounds after a weeklong drug break. But these rebounds proved more consistent than in Dybul's study. Guenthard looked at 14 people who had frequent viral load measures during SSITT's five treatment breaks. The first four breaks lasted two weeks, and the final break was open ended. Eight days after the STIs started, 11 of 14 people (79 percent) had a rebound from under 50 to over 100 copies/mL. At the two-week point, 12 of 14 people (86 percent) had rebounds above 100 copies/mL. The SSITT team published these data shortly before the meeting.<sup>28</sup>

Guenthard allowed that differences between regimens in SSITT and Dybul's NIAID study may account for the more consistent rebounds in SSITT. No one in SSITT took a boosted PI, while everyone in NIAID took indinavir plus ritonavir (800/100 mg twice daily). But the HIVNAT study used ritonavir-boosted saquinavir, and the HIVNAT team counted seven breakthroughs above 1,000 copies/mL in 26 week-on/week-off participants

(27 percent). Guenthard concluded that, "although conceptually intriguing," week-on/week-off cycling "can only be safely performed in rigorously controlled clinical trials and in patients who have never failed treatment before." In his slide talk at the 10th CROI, Dybul made the same point, noting that week-on/week-off therapy will not be easy in practice: "We know you may get into trouble."

Two other fixed-period cycling studies got PowerPoint treatment at the 10th CROI, one by NIAID's Dybul [abstract 681b]. This randomized trial of continuous HAART versus four-weeks-off/eight-weeks-on showed a certain risk—resistance—and little if any benefit for these longer drug breaks. Study participants all started with a viral load below 50 copies/mL and a CD4 count topping 300 cells/mm<sup>3</sup>, and they could take either a PI or an NNRTI.

Three of eight people taking breaks from efavirenz endured the emergence of the class-killing K103N mutation. Two of them also picked up the M184V change favored by 3TC. One person taking a break from PI therapy ended up with M184V, and one got the thymidine analog mutation T215Y. (The shorter, two-week breaks in SSITT spawned M184V mutants in eight of 21 people who had to leave the study because they couldn't regain sub-50 viral control, Guenthard noted.)

At week 48 of the NIAID study—after the fourth "on" cycle—the STI group didn't differ from the continuous treatment group in:

- Triglycerides
- Total or LDL cholesterol
- The heart disease marker C-reactive protein
- The liver enzymes AST and ALT

At weeks 40 and 48 the groups didn't differ in signals of immune stimulation, such as HIV-specific CD4 cells or CD4 or CD8 cells with the CD25 marker. People in the STI arm did have significantly higher levels of activated CD8 cells reflected in CD38 and DR markers at weeks 40 and 48, but no one can say whether that difference will translate into immunologic or virologic benefits. Indeed, at study week 48, two of 22 people (9 percent) in the steady treatment group had a viral load above 50 copies/mL,

compared with five of 19 (26 percent) in the STI arm.

Guenthard also outlined a published SSITT report that charted no immune boost with the two-week-on/four-week-off strategy.<sup>29</sup> The STIs did lift HIV-specific cytotoxic T-lymphocyte responses, but only to pretreatment levels. And those responses did not correlate with control of viremia. Among 14 people who stayed off treatment for two years during SSITT's final drug break, the average CD4 count shed 76 cells/mm<sup>3</sup> yearly—precisely the average yearly loss among people who never start therapy. “There is nothing magic about these STIs,” Guenthard counseled. “This [CD4 drop] is just natural history.”

The second randomized, fixed-cycle study came from Stefano Vella at the Istituto Superiore di Sanità (ISS) in Rome [abstract 66]. After three treatment breaks of one, one, and two months, this ongoing trial saw a slow, steady accretion of new resistance mutations in reverse transcriptase and protease.

Vella hopes to randomize 300 people with a CD4 count above 350 cells/mm<sup>3</sup> (nadir above 100 cells/mm<sup>3</sup>) and a viral load below 400 copies/mL to continuous therapy or cycles of one, one, two, two, and three months off treatment, each interleaved with three months on. About two thirds of study participants are taking an NNRTI. As in Dybul's study, the nonnuke is stopped a few days before the nukes to compensate for its longer half-life. Also as in Dybul's study, that trick didn't work for everyone. The rate of new nonnucleoside-specific mutations rose from 2 percent after the first STI to 6.3 percent after the third STI (Table 7). Mutations that topple NRTIs and PIs also grew apace.

Most people in the STI arm regained viral control after each drug break. But the people who sailed through the drug holiday without meeting a new mutation did better virologically. After the first, second, and third STIs, 95.7 percent, 91.5 percent, and 100 percent with no new mutations pushed their viral load back under 400 copies/mL. Respective percentages among people who picked up new mutations were 91 percent, 88 percent, and 92.3 percent.

Vella's study demonstrates that PIs are not resistance-proof during STIs—at least if the on-treatment goal is 400 copies/mL

**Table 7. New mutations in a fixed-length STI trial**

	After 1st STI (1 month long)	After 2nd STI (1 month long)	After 3rd STI (2 months long)
<i>n</i>	130	126	36
NRTI mutations (%)	8.0	8.8	9.7
NNRTI mutations (%)	2.0	5.5	6.3
PI mutations (%)	5.1	3.7	8.1

Source: Stefano Vella, abstract 66.

instead of 50 copies/mL. Only one other STI trial known to this reporter saw the emergence of protease resistance—a single case in SSITT.<sup>30</sup> The NIAID, ISS, and SSITT studies—and others<sup>31,32</sup>—amply demonstrate that the greatest resistance risk during drug breaks lies with nonnucleosides and 3TC.



### Three presalvage STI studies

Three Retrovirus studies explored treatment breaks before salvage in different populations, and they reached two different conclusions. Christine Katlama (Pitié-Salpêtrière Hospital, Paris) came to CROI with 48-week results from the GIGHAART trial, which randomized people to stop drugs before salvage or to start a salvage regimen immediately [abstract 68]. The virologic advantage she saw for the STI group at week 12 had lost statistical significance at week 24—perhaps a certain upshot in people with advanced disease asked to take a mega-HAART regimen. But before considering Katlama's results, consider two studies that found no advantage—and in one case a disadvantage—for drug holidays before rescue therapy.

In the randomized CPCRA study 064, disease progression or death—the primary endpoint—proved 2.6 times more likely in people who took a presalvage STI than in those who didn't ( $P = 0.01$ ) [abstract 67]. After a median follow-up of 11.6 months, each group had the same number of deaths: eight.

Jody Lawrence (University of California, San Francisco) and the CPCRA team aimed to recruit 480 people with multidrug-resistant virus, but the Data Safety and Monitoring Board closed enrollment with 138 people in the STI arm and 132 in the immediate treatment arm when it became clear that the study would not hit its target—a 33 percent lower progression rate in the STI group. People randomized to stop their drugs did so for four months before starting a new regimen picked with the help of resistance assays. The no-STI group began their resistance-guided regimens immediately. The STI group averaged 3.6 drugs in the salvage regimen, 2.7 of them rated active; the control arm started an average 3.8 drugs, 2.8 of them rated active.

The mean starting viral load stood at 100,000 copies/mL; 26 percent of enrollees had a CD4 count under 50 cells/mm<sup>3</sup>, 37 percent between 50 and 200 cells/mm<sup>3</sup>, and 37 percent over 200 cells/mm<sup>3</sup>. Nearly half had triple-class resistance, and nearly half had an AIDS-defining disease on their chart.

The wager in stopping drugs before salvage is that a person's unruly and resistant viral swarm will assume a more drug-sensitive demeanor during the holiday while that person stays one step ahead of new AIDS diseases. In one sense that wager paid off. Lawrence explained that trial planners opted for a four-month holiday to foster optimal emergence of drug-sensitive virus. And 64 percent in the STI group did enjoy reversion to wild-type virus during the four-month

**Table 8. HIV disease progression or death in CPCRA 064**

	STI group (n = 138)	No-STI group (n = 132)
Persons with progression or death	22*	12*
Death†	8	8
Esophageal candidiasis	7	1
<i>P. carinii</i> pneumonia	4	0
Cryptosporidiosis	3	1
Lymphoma	2	0
Cytomegalovirus	1	1
<i>M. avium</i> complex	0	1
Herpes simplex virus	0	1

\* $P = 0.01$ .

†Most deaths were AIDS related.

Source: Jody Lawrence, abstract 67.

break, usually without disease progression. Most new AIDS diagnoses came not during the STI, but after people resumed therapy.

Yet despite this high rate of reversion to drug-susceptible virus, the STI group gained nothing in long-term virologic control. At month 12, eight months after they restarted therapy, their mean viral load stood 0.76 log below baseline compared with 0.66 log in the no-STI group—not a significant difference. And average viral loads for the two groups stayed close through study month 20. At month eight, four months after the STI group resumed treatment, about 22 percent had a viral load under 400 copies/mL compared with about 8 percent in the control group. Those sub-400 rates closed to 18 percent for the STI group and 11 percent for controls at month 12, and to 15 percent for the STI group and 12 percent for controls at month 16. (A randomized Spanish trial of presalvage STIs also found little virologic difference between study arms. See note 33.)

The more telling difference between the STI and control arms involved CD4 cells. After the four-month treatment break, the average CD4 count had dropped about 50 cells/mm<sup>3</sup> in the STI group while rising about 40 cells/mm<sup>3</sup> in the immediate-treatment arm ( $P < 0.001$ ). In the immediate group that gain persisted through 20 months of follow-up. Meanwhile, the average count in the STI arm climbed back to baseline by month six (treatment month two) ( $P < 0.001$  versus the control group). But CD4 counts in the STI group barely inched above baseline

through week 20 ( $P = 0.06$  versus the control arm at week 20). That consistently lower CD4 count in the STI arm probably accounts for their higher rate of disease progression. Most of the AIDS diagnoses in either arm were not life threatening, but some nastier “events” turned up in the STI group (Table 8).

Six-week analysis of an ongoing presalvage drug break study by the California Collaborative Treatment Group (CCTG) found a significantly deeper viral load drop among people who resumed treatment with lopinavir after a break than among those who started lopinavir immediately. But statistical analysis of baseline variables wiped out the drug holiday’s apparent advantage.

CCTG 578 enrolled 16 people who started salvage lopinavir immediately and 14 who started after a four-month or longer drug holiday. Beginning at treatment week two and persisting through week six, the treatment break group had a significantly bigger viral load dip than the immediate treatment group—2 logs versus 1 log at week six ( $P \leq 0.02$ ). But Richard Haubrich (University of California, San Diego) suspected the deeper viral dive among the break takers might reflect their higher baseline viral load—5.2 logs versus 4.5 in the other group ( $P < 0.05$ ). In two multivariate models that accounted for baseline viral load, taking a treatment break did not independently favor a bigger viral load drop at week six.

Three other baseline factors may have favored the drug holiday group: Everyone taking a break had two or more active

drugs available for the salvage regimen, compared with 12 of 16 people in the immediate treatment group. The baseline fold-change in resistance to lopinavir measured 0.7 in the interruption group and 2.3 in immediate group. And the baseline inhibitory quotient (lopinavir trough/50 percent inhibitory concentration) was higher in the holiday group (26) than in the other group (17). Haubrich concluded that his findings “do not support the use of treatment interruption for improving viral load responses in treatment-experienced patients.”

Then there is GIGHAART, which showed at least a short-term (12-week) virologic bonus with drug holidays before megadrug salvage [abstract 68]. Five things distinguish GIGHAART from the other randomized presalvage study at CROI, the CPCRA trial:

- CPCRA was bigger, enrolling 270 people versus 68 in GIGHAART.
- CPCRA used a four-month STI versus two months in GIGHAART.
- CPCRA’s STI group included 64 percent with reversion to more drug-sensitive virus compared with 48 percent in GIGHAART’s STI arm.
- CPCRA typically used a four-drug regimen, versus eight or nine drugs in GIGHAART.
- CPCRA enrolled people with less advanced disease.

In GIGHAART the baseline CD4 count averaged about 27 cells/mm<sup>3</sup>, compared with 180 cells/mm<sup>3</sup> in CPCRA. Such profound differences make comparing these studies maddening, if not impossible.

GIGHAART’s bottom line remains what it was when Katlama unveiled early results in Athens on October 30, 2001: In people like these an eight-week drug break does significantly better than immediate treatment in clinching the primary endpoint—at least a 1-log viral load drop at treatment week 12. In an intent-to-treat analysis, Katlama reported at the 10th CROI, 62 percent in the STI group and 26 in the control group had at least a 1-log RNA drop at week 12 ( $P = 0.007$ ).

The question for clinicians (and people tempted to try this tactic) also remains what it was in Athens: Does this 12-week difference mean anything clinically? If one looks at the sternest endpoint—

death—the answer is no. After 48 weeks of treatment, two people in each study arm had died. When one considers progression or death, GIGHAART results nearly parallel CPCRA results, with about twice as many clinical setbacks in the STI arms. When Katlama detailed these results at the XIV International AIDS Conference in July 2002, 10 people in the STI group hit clinical snags versus six in the immediate-treatment group (see note 34).

A third clinical factor—drug tolerability—must also figure in any analysis of kitchen-sink regimens taken by people with advanced disease. After 48 weeks of treatment, only 47 percent in the STI group and 22 percent in the control group were still taking more than six antiretrovirals. The lower rate in the immediate-treatment group, Katlama told *IAPAC Monthly*, reflects their weaker virologic response. People whose viral load doesn't fall much see little reason to keep taking nine drugs. Most people in both groups, she said, stuck with most of their drugs through 24 weeks. Yet the between-group difference in proportions with more than a 1-log viral load drop lost statistical significance by week 24: 50 percent in the STI group and 24 percent in the control group ( $P = 0.08$ ) in an intent-to-treat analysis. For people still on treatment at 24 weeks, the rates weren't much different: 55 percent versus 26 percent.

Did reversion to a more drug-susceptible virus help people in GIGHAART's STI arm? Yes, if "help" means at least a 1-log viral load drop by week 12. Eight of 16 people (50 percent) in the STI group with no reversion lost at least a log of RNA by week 12, compared with 12 of 14 (86 percent) who had some reversion. In a multivariate analysis, taking an STI without reversion raised the odds of 12-week success 3.2 times compared with the immediate treatment group, while taking an STI and achieving some reversion raised those odds 12.4 times. Yet only one of the 14 reverters had a complete return to wild-type virus. The others lost one or more major PI, NNRTI, or NRTI mutations. Katlama suggested that only a few reversions may help people with multidrug-resistant virus—if they start a GIGHAART regimen.

Would Katlama try GIGHAART after an STI in other people with a baseline dilemma matching those in this trial?

"Yes," she told *IAPAC Monthly*. Whether others follow that advice depends on what they hope to gain. If it's a longer, healthier life for people with tome-like treatment histories, it's impossible to escape Huldrych Guenthard's conclusion in the 10th CROI's last talk: "There is no clinical benefit proven [for] STIs before salvage therapy." ■

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

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## A B S T R A C T S

### Intervirology

#### Effects of multiple virus coinfections on disease progression in HIV-positive patients

B Shieh et al.

**OBJECTIVE:** Since virus infections in AIDS patients are mostly inevitable and as they frequently cause disease deterioration and therapeutic failures, a comprehensive investigation was made of the influence of the coinfections of nine well-known viruses on disease progression in patients infected with human immunodeficiency virus type 1 (HIV). **METHODS:** A cross-sectional study of 62 HIV-positive patients was conducted to correlate the prevalence rates for the nine viruses with the alanine aminotransferase (ALT) levels and CD4 cell counts of the patients. **RESULTS:** The rates of HIV-positive patients infected with the nine viruses are significantly higher than those of the control groups. Furthermore, almost one third of the patients in the studied group was coinfecting with transfusion-transmitted virus (TTV) and manifested significantly higher ALT levels ( $p = 0.020$ ), and these were raised further if coinfection with TTV and human hepatitis C virus had occurred ( $p = 0.010$ ). By analyzing CD4 cell counts, the only significant effect on AIDS progression which could be detected was coinfection with human herpesvirus 8. **CONCLUSION:** This result confirmed that immune-suppressed persons are more vulnerable to common virus infections. Unlike hepatitis B or C virus, TTV seems to accelerate the progression of chronic hepatitis in HIV-infected patients.

*Intervirology* 2003;46(2):105-13.

### Archives of Pathology and Laboratory Medicine

#### Results of a physician survey on ordering viral load testing

LK Hofherr et al.

**OBJECTIVE:** To profile physicians' practices, utilization, and understanding of human immunodeficiency virus type 1 RNA (viral load) testing and the laboratory's role in this testing. **DESIGN:** Cross sectional study using a 34-item self-report survey mailed to physicians identified as requesting viral load testing, with follow-up mailings to nonresponders. **PARTICIPANTS:** A sampling of US physicians specializing in infectious diseases, internal medicine, and family practice associated with high, medium, and low human immunodeficiency virus/acquired immunodeficiency syndrome incidence areas. **RESULTS:** Most respondents using viral load results were infectious diseases specialists practicing in urban areas. The reasons most frequently given for requesting viral load testing were 1) to assist in patient follow-up or monitoring (75.4 percent), and

2) to initiate/guide therapy (62.5 percent). Respondents indicated that the interpretation and use of viral load results presented difficulty in the areas of patient treatment and in determining what change from baseline was clinically significant. Few respondents used the testing laboratory pathologist as a resource for interpreting viral load test results. **CONCLUSION:** Our study indicates that physicians have questions about 1) the meaning of viral load tests, 2) how often to monitor the viral load, and 3) what change from baseline of the viral load is significant. Few physicians avail themselves of the expertise available in the laboratory for testing viral loads and interpreting such results.

*Arch Pathol Lab Med* 2003;127(4):446-50.

### HIV Clinical Trials

#### Effect of protease inhibitor-based highly active antiretroviral therapy on survival in HIV-associated advanced Kaposi's sarcoma patients treated with chemotherapy

H Leitch, M Trudeau, and JP Routy

**OBJECTIVE:** To determine whether the use of protease inhibitor (PI)-based antiretroviral (ARV) therapy had an impact on the survival of patients with human immunodeficiency virus (HIV) infection-associated Kaposi's sarcoma (KS) who were receiving systemic chemotherapy. **METHOD:** Records of 48 AIDS patients with extensive KS who received chemotherapy from 1995 to 1999 were reviewed. Analysis by presence or absence of PI treatment was undertaken, and patients who were receiving nonnucleoside reverse transcriptase inhibitors (NNRTIs) were excluded from the analysis. **RESULTS:** Median age was 38 years, and 47 patients were men having sex with men. Half of the patients (54 percent) had at least one prior AIDS-defining event. Median CD4 count at diagnosis of KS was 28 cells/ $\mu$ L (range, 1-625). Visceral KS was present in 33 patients (69 percent), and the remainder of patients had extensive and symptomatic cutaneous and/or mucous membrane involvement. All patients received at least one cycle of chemotherapy, including vincristine/bleomycin or an anthracycline-containing regimen. There was a significant difference in the median survival (MS) between the 28 patients (58 percent) treated with PI-based antiretroviral therapy (31 months [range, 1.8-48]) and the group not receiving PI (seven months [range, 1-28],  $p = .0001$ ). In addition, 81 percent of patients in the PI group were alive at 18 months from initiation of chemotherapy versus 12 percent in the non-PI group. Twenty patients (71 percent) in the PI-treated group were able to discontinue chemotherapy for at least one month after remission of KS, in comparison to 3 of 20 (15 percent) patients in the group of patients who did not receive PI

( $p = .00001$ ). Death due to KS occurred in six of 28 (21 percent) patients (total nine deaths) in the PI group and 14 of 20 (70 percent) patients (total 18 deaths) in the non-PI group ( $p = .001$ ). **CONCLUSION:** In a nonselected group of patients with advanced and extensive KS in a real-life clinical setting, our results show a survival benefit and a decrease in KS-related death for patients receiving chemotherapy and PI-based ARV therapy when compared to patients not receiving PI-based therapy. Discontinuation of chemotherapy in patients receiving PI-based antiretroviral therapy appears to be feasible in patients who attain remission of KS.

*HIV Clin Trials* 2003;4(2):107-114.

### Journal of Acquired Immune Deficiency Syndromes

#### Immune deficiency and risk for malignancy among persons with AIDS

SM Mbulaitaye, RJ Biggar, JJ Goedert, and EA Engels

**BACKGROUND:** People with AIDS have an elevated risk for cancer. We studied the relationship between cancer risk and AIDS-related immunosuppression as measured by CD4 count at AIDS onset. **METHODS:** We linked records from AIDS and cancer registries in 11 US regions (1990-1996). We studied 82,217 (86.6 percent) adults who had a CD4 count measured at AIDS onset and survived into the follow-up period. We calculated standardized incidence ratios (SIRs) for AIDS-defining (Kaposi sarcoma [KS], non-Hodgkin lymphoma [NHL] and cervical cancer) as well as non-AIDS-defining cancers in the two years after AIDS onset. For each cancer, the change in SIRs across CD4 counts (0-49 cells/ $\text{mm}^3$ , 50-99 cells/ $\text{mm}^3$ , 100-199 cells/ $\text{mm}^3$ , and  $\geq 200$  cells/ $\text{mm}^3$ ) was modeled using Poisson regression. **RESULTS:** The SIRs for KS, NHL, and cervical cancer were 258, 78, and 8.8, respectively. For each fall of 100 CD4 cells/ $\text{mm}^3$ , RRs were 1.36 (95 percent CI: 1.29-1.43) for KS and 1.48 (95 percent CI: 1.37-1.59) for NHL. Among NHL subtypes, the association with lower CD4 counts was strongest for immunoblastic lymphoma (RR = 1.64, 95 percent CI: 1.37-1.96, per decline of 100 CD4 cells/ $\text{mm}^3$ ) and central nervous system lymphoma (RR = 2.29, 95 percent CI: 1.95-2.69). The SIR for cervical cancer did not vary with CD4 count ( $p = .74$ ). For non-AIDS-defining cancers (overall SIR = 2.1), neither the combined risk nor the risk of specific types was associated with declining CD4 counts. **CONCLUSION:** KS and NHL risk increased with level of immunosuppression at AIDS onset. Risks for other cancers, including cervical cancer, were unrelated to CD4 counts. Elevated risks for non-AIDS cancers may be a result of lifestyle factors.

*J Acquir Immune Defic Syndr* 2003;32(5):527-33.



## I N T H E L I F E



### Samson Mijoro-Odida

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

This month, *IAPAC Monthly* is proud to feature Samson Mijoro-Odida, who is Principal Medical Officer at the Okahao State Hospital in Namibia.

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

The world is full of natural resources and mental resources, including mine... The mental resources could be used to guarantee peace for all and equitably distribute the wealth to all, but the shame is that these resources are used to keep the poor poorer and destroy the vulnerable.

#### What activities, avocations, or hobbies interest you?

My hobbies are reading international affairs and continuing medical education on a daily basis.

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

If I was to live anywhere I would like the place to be in Africa, because the pollution is the lowest and there is, compared to other continents, less crime and less racism.

#### Who are your mentors or real life heroes?

President Sam Nujoma of the Republic of Namibia, because of the open democratic government he has in place where every citizen is seen to be directly benefiting from the government services up to the village level. The districts and regions budget for their own development and his government ensures equitable distribution of the resources according to the budget. The other person is United Nations Secretary-General Kofi Annan, for his ability to be cool, calm, and collected while solving world problems.

#### With what historical figure do you most identify?

Mwalimu Julius Nyerere of Tanzania because of the wise leadership quality with which he has led Tanzanians out of the quagmire of tribalism.

#### Who are your favorite authors?

My favorite authors are William Shakespeare and Chinua Achebe.

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

I would choose to live during the present period of history because it is beaming with knowledge and so much can be learned with modern science and technology despite the limited lifespan of the people.

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

I would have likely become a lawyer.

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

The greatest achievements of humanity are the advancement of science and technology, the spread of the three R's—Reading, writing, and arithmetic. The greatest failures are the failure to reduce the gap between the rich and the poor and the failure to live in peace with one another throughout history, hence banishing wars.

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

My prediction is that 10 years from now the poor will be even poorer and the rich will be richer, and therefore with poverty, peace will not be guaranteed for all. The weather will be warmer, if care is not taken to stop further depletion of the ozone layer. Ten years thereafter the rich will start distributing wealth to improve the livelihood of the poor upon realizing that their (the rich's) insecurity is made worse by exploiting the poor. All nations will therefore come closer than they have ever been in history. ■



SAY ANYTHING



**How long are we going to toyi-toyi (picket) before we get treatment? People are dying because of anger and frustration.**

Beauty More, an HIV counselor who worked with 32-year-old Kenareng Moyeketsi, during Moyeketsi's emotionally charged funeral April 1, 2003. Moyeketsi was the first to die of more than 200 activists, most of them HIV-positive, who leveled charges of "culpable homicide" against South African Minister of Health Manto Tshabalala-Msimang and Trade Minister Alec Erwin for stalling a government plan to provide antiretroviral drugs to people living with HIV/AIDS. According to Reuters, more than 300 activists and friends, many wearing T-shirts with the message "Dying for Treatment," buried Moyeketsi, who died in late March 2003. During the funeral, activists claimed her death highlights the plight of many young, black South African women and vowed to carry on with a civil disobedience campaign until their demands for antiretroviral drugs are met.

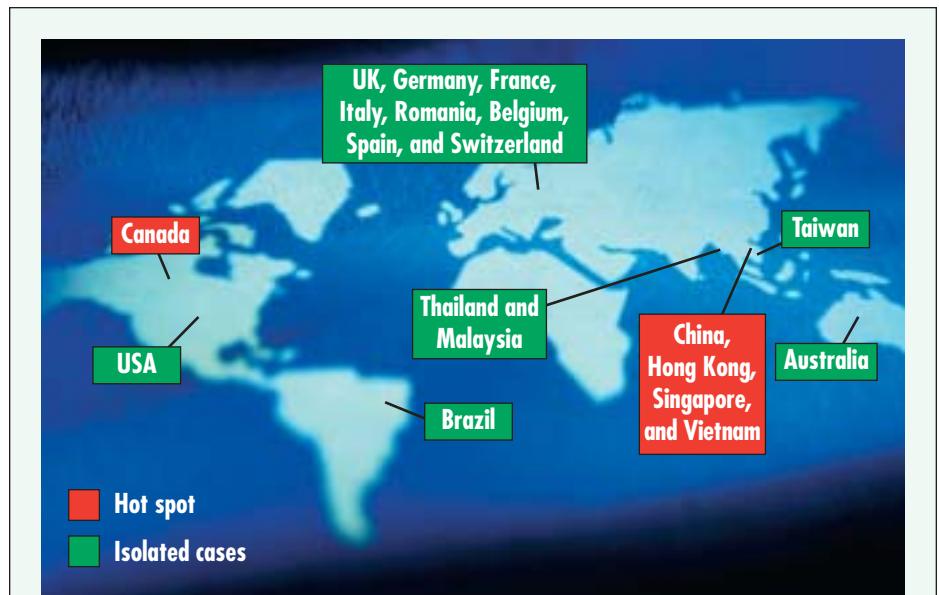


**It has traditionally been more difficult to raise funds for situations that are perceived as open-ended, intractable and hopeless.**

Kris Janowski, a spokesman for the UN High Commissioner for Refugees (UNHCR), quoted as a source in an April 11, 2003, Wall Street Journal article entitled, "US Diverts Relief Funds to Prepare for Iraq Needs." According to the article, donor nations have been withholding funding for other regions to preserve their ability to fund Iraqi relief. For example, a United Nations Children's Fund (UNICEF) appeal in January 2003 for US\$501 million in "emergency relief" for 30

countries has yielded less than US\$125 million, or 23 percent. At the same time last year, UNICEF had raised 37 percent of its emergency appeal. The article's authors report that the United States has diverted more than US\$500 million from relief efforts to prepare for the aftermath of the war in Iraq. While the White House

plans to repay most of the money diverted from other accounts within the US State Department's foreign-aid budget, the Bush Administration is said to be planning to dip into other foreign-aid accounts to free more than US\$100 million in additional funds for Iraq-relief efforts.



**There are a lot of links between SARS and AIDS... All of the criticism which has been levied at the Chinese government's healthcare system on the SARS issue, can easily be applied to the HIV/AIDS problem.**

Bates Gill, who holds the Freeman Chair in China Studies at the Center for Strategic and International Studies (CSIS) and who is Co-Editor of a recent CSIS report entitled, "Averting a Full-Blown HIV/AIDS Epidemic in China," as quoted in an April 9, 2003, United Press International wire story.

Gill said that although HIV/AIDS is approaching critical mass in China, the Chinese government is not affording the problem the kind of attention it deserves. According to Gill, the Chinese government's initial denials that the country had a significant outbreak of severe acute respiratory syndrome (SARS) and was the source of the epidemic, along with its slow response to addressing the resulting public health crisis, is typical of China's official responses to disease.