

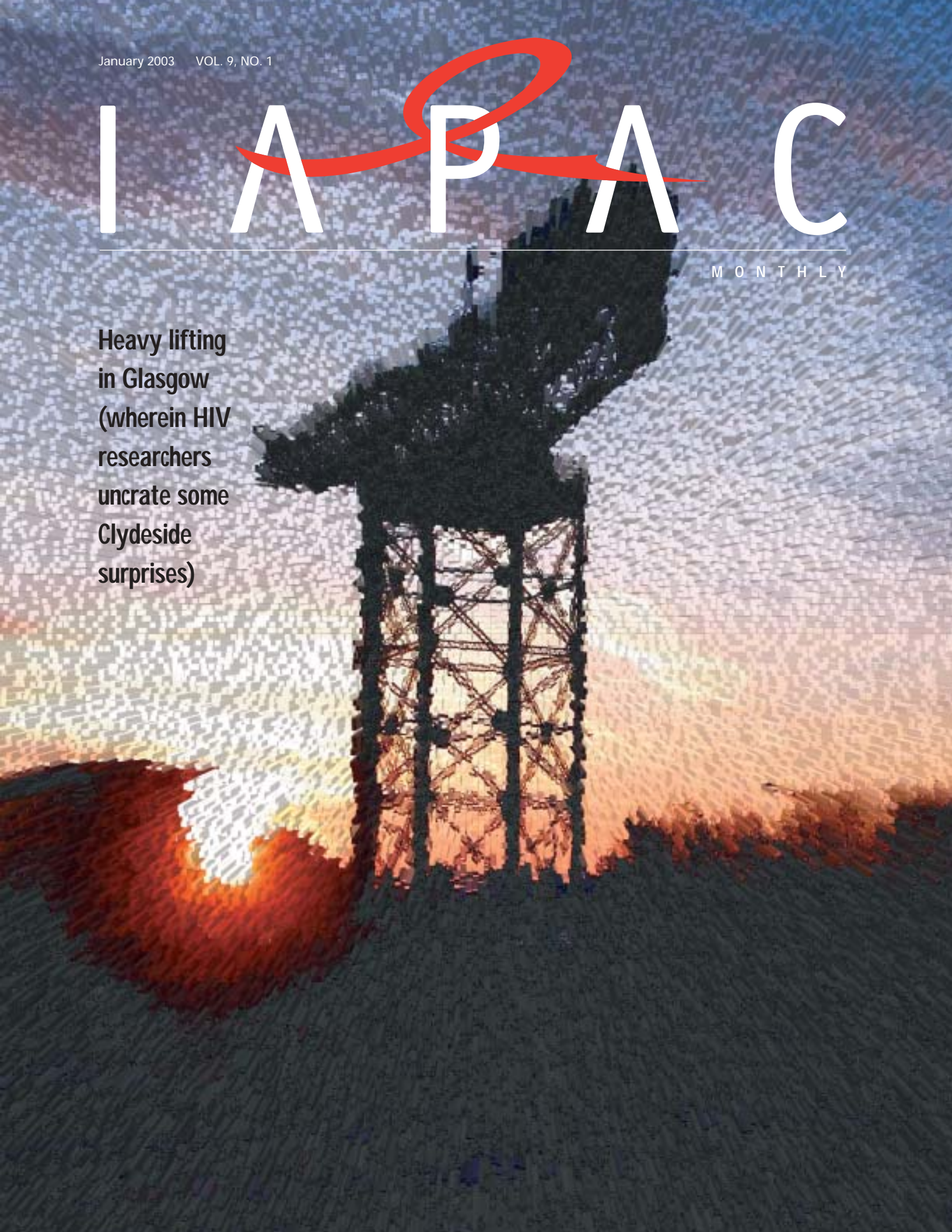
January 2003 VOL. 9, NO. 1


I A P A C



M O N T H L Y

**Heavy lifting
in Glasgow
(wherein HIV
researchers
uncrate some
Clydeside
surprises)**



A young girl with curly hair, wearing a light-colored, long-sleeved dress, sits on a metal container in a grassy area. She is looking down at something in her hands. The background shows tall, multi-story apartment buildings with many windows. The scene is outdoors, and there is some trash scattered on the grass.

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8

Heavy lifting in Glasgow (wherein HIV researchers uncrate some Clydeside surprises)

Mark Mascolini



After a year of meetings rife with HIV treatment news, how much can you expect from the Glasgow congress? Plenty. Pharmacokinetic curiosities included d4T triphosphate in people taking AZT, and indinavir/ritonavir lite—400/100 mg twice a day. A clutch of clinic reports agreed that long responders are replacing nonresponders, while other studies showed how T-cell counts sway STI results. New drugs on the agenda included T-20, atazanavir, and amprenavir's prodrug.

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

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

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Routing out indifference

José M. Zuniga

“The world sleeps in the face of the greatest disaster to face Homo sapiens in recorded history. Future historians will marvel.”

The failure to mount a global response in proportion to the threat posed by the AIDS pandemic was characterized recently by Richard Feachem, Executive Director of the Global Fund to Fight AIDS, Tuberculosis, and Malaria, in no uncertain terms and in a way that should make each of us stop and think.

It is not the case—and neither, I am certain, did Feachem mean to say—that nothing is being done. Despite all of our current efforts, however, we know that we are not doing enough. We are aware that tens and even hundreds of millions of people will suffer and die unnecessarily if we do not increase global and national efforts to prevent infection and treat those already infected. And, thus, Feachem is correct; if more is not done, future historians will certainly look back at this time with a sense of horrified awe. As has been the case with other preventable tragedies of world historical proportion, the chroniclers of the AIDS pandemic will look back through the years, decades, and centuries to ask, “Why did the people of the world not do more?”

Similar to the way in which certain images have come to stand for past tragedies, I suspect that the AIDS pandemic, if the world does not fully do what it must, will be remembered in symbols that sit in society’s collective minds’ eye as haunting reminders of cruelty and indifference. In Rwanda we think of rivers choked with bludgeoned corpses. For the atrocities of the Khmer Rouge, one recalls photographs of heaping mounds of sun-bleached skulls. The gas chambers of



Auschwitz symbolize one of the modern world’s most notorious examples of senseless destruction, the Nazi Holocaust. And, I fear that news reports coming out of South Africa last month describe a circumstance that might become, as with these others, an image shocking to future generations because it represents the failure to prevent preventable suffering: the municipal government of Johannesburg is considering a plan to bury in abandoned mineshafts the thousands felled by AIDS whose corpses cannot be accommodated in the city’s rapidly filling cemeteries.

As reported in the British magazine *New Scientist*, “Old gold mines could be converted into underground streets lined with tombs, accessed from ground level by lifts.” Alan Buff, the head of Johannesburg’s public cemeteries, believes that this or other drastic measures have become

inevitable. He stated that Johannesburg, whose citizens eschew cremation, must plan to bury 70,000 people each year by 2010, several times more than the 20,000 people (already a greatly increased number) who were interred in 2002.

What will these numbers be like by mid-century, when epidemiologists predict that the pandemic, continuing its current trajectory, might finally peak? What will they be like in Bombay and Beijing, two cities where AIDS will likely infect millions in years ahead? And when the people of the world know the answers to these questions, will they look back at eerie tunnels filled with the bodies of young South Africans who died from a disease that is preventable and treatable and ask why it was allowed to happen?

We must do all within our power to avoid this human catastrophe. When we count on such information and ability as we possess today, we have no moral recourse but to act now. Failing to prevent a death, when preventing that death is entirely within one’s ability, is tantamount to an abrogation of our collective humanity. The same is true on a global scale, so that if the world allows countless millions to suffer and die from HIV disease, it will be an act of moral depravity approaching that of genocide. We cannot let this possibility come to pass. Let us rout out indifference and choose the path of compassion and action. Let us recognize and be brought to indignation now by the signs of suffering that are in our midst—lest they come back as terrible symbols to haunt us and our world for generations to come. ■

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



I N T H E N E W S

IAPAC commits to 'fast action' in face of global challenges

Scott A. Wolfe

During its annual meeting December 13, 2002, the Board of Trustees of the International Association of Physicians in AIDS Care (IAPAC) unanimously voted to extend the contract of President José M. Zuniga for a second three-year term. According to IAPAC Board of Trustees Chair Allen I. Freehling, “the reappointment reflects the strong leadership demonstrated by Zuniga throughout his tenure at the association’s helm, and the tremendous growth and diversification of programs and staffing that he has achieved within that time.”

Since December 1999, at which point Zuniga assumed his current role, IAPAC has realized greatly increased global membership numbers; has opened regional offices in southern Africa and Europe; has significantly expanded programmatic activities; and has increased the size and diversified the composition of both its Board of Trustees and international staff.

“I am pleased to carry the ultimate responsibility for ensuring the solvency and efficacy of the International Association of Physicians in AIDS Care,” said Freehling. “José’s reappointment to this critical leadership position reflects our respect for the accomplishments of his first three years, and our confidence that he will continue to ensure that this association, its staff, and allies realize their full and collective potential in redressing the global AIDS pandemic. This is what is demanded of an effective leader.”

Slate of Officers elected

Other business transacted during the December 13, 2002, annual meeting of the IAPAC Board of Trustees included the election of Officers—required by IAPAC Bylaws to take place every two years.

Freehling, who is Executive Director of the City of Los Angeles’ Human Rights



Allen I. Freehling



Carol A. Harris



Gloria Varona Williams



Rubin Philip

Commission, was re-elected to serve another term as Chair of IAPAC’s Board of Trustees. The three other elected Officers include: Carol A. Harris of Albert Einstein College of Medicine in New York to serve as Vice Chair; Gloria Varona Williams of Chicago to serve a second term as Treasurer; and Ruben Philip, Anglican Archbishop of KwaZulu-Natal Province in Durban, South Africa, to serve as Secretary.

Zuniga praised the newly elected slate of Officers for their ongoing commitment to IAPAC’s mission and vision.

“IAPAC is blessed with a group of highly dedicated and motivated volunteer leaders who comprise our Board of Trustees—among them our Founding Chair, Allen Freehling,” Zuniga said. “I am certain that with this newly elected slate of Officers our operational and programmatic goals

for 2003 and beyond will be met in the spirit of accountability and transparency.”

Freehling and Zuniga commended the contributions of former Vice Chair D. William Cameron of the University of Ottawa, Canada, whose term on the IAPAC Board of Trustees ended in October 2002. Cameron continues his affiliation with IAPAC as Editor of the quarterly peer-reviewed clinical journal *JIA PAC*, and as Co-Chair of the Global AIDS Learning & Evaluation Network (GALEN) Curriculum Committee.

FY2003 workplan, budget approved

In addition to solidifying IAPAC’s leadership structure, the Board of Trustees also approved IAPAC’s workplan and budget for 2003. IAPAC’s 2003 budget, which

Continued on page 7



P E R S P E C T I V E

Time to move on HIV/AIDS treatment and care

*Bernhard Schwartländer
and Joep MA Lange*

The number of people living with HIV/AIDS has now reached 42 million, 95 percent of whom live in developing countries. Antiretroviral drugs could dramatically alter the prognosis for millions of these people, but the number who can currently access them remains unacceptably low, estimated at around 300,000 people at the end of 2002, a mere 5 percent of the estimated 6 million adults presently in need. In sub-Saharan Africa, only 1 percent of those in need are receiving antiretroviral therapy.

Current opportunities to scale up HIV treatment and care are immense, with many of the pieces necessary to make HIV treatment a reality now falling into place. Simplified regimens mean that a public health approach—rather than an individualistic approach—can include many more people on treatment. Antiretroviral drug prices have fallen on average 85 percent in developing countries over the last three years, while global expenditure on HIV/AIDS has increased from just US\$300 million in 1999 to nearly US\$3 billion in 2002. Donors (including the World Bank, and the Global Fund to Fight AIDS, Tuberculosis, and Malaria) are increasingly willing to support HIV treatment and care as part of comprehensive programs, and there is growing commitment to treatment and care on the part of developing countries themselves, as they realize that treatment and care are essential components of a stronger, more effective response to the epidemic.

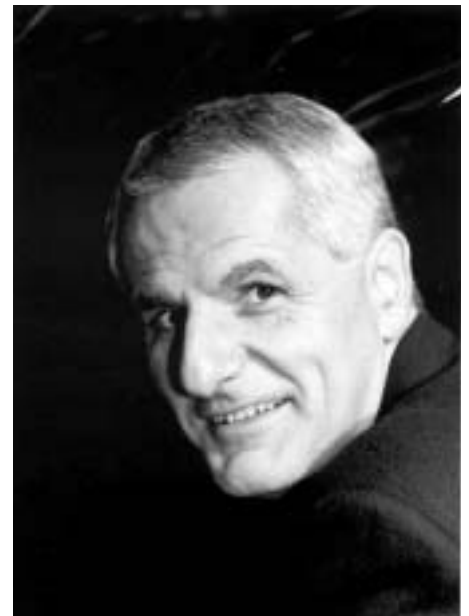
The United Nations has set a global



Bernhard Schwartländer

goal of expanding HIV treatment from the current 300,000 to at least 3 million people with HIV/AIDS in developing countries by 2005. Although this may seem daunting, it can be accomplished if, for every person currently on treatment, just one or two more can be enrolled in treatment programs, every year, between now and 2005.

Although it is true that more resources, infrastructure and lower drug prices are necessary, this cannot be used as an excuse for inaction. Real opportunities exist now to introduce antiretroviral therapy in existing health services as a basis for the rapid implementation of treatment programs. In addition to traditional hospital-based services, antenatal, child health, sexually transmitted infection (STI) and tuberculosis services can serve as key



Joep MA Lange

entry points for HIV treatment and care. It is also essential that programs to prevent mother-to-child transmission of HIV address the treatment needs of women and their families as well. In the private sector, leading businesses and other employers are already joining the fight against HIV/AIDS by initiating HIV treatment and care programs for employees and their family members. Although they cannot substitute for major public programs, such initiatives can and must play a more important role.

Of course, notwithstanding these opportunities, unprecedented challenges remain. There is still much that remains unknown, and some major issues—such as drug prices and procurement, human resources and provider training—

are beyond the capacity of any one organization to solve. It is clear that the current momentum can only be maintained through a determined effort by the international community to share expertise, coordinate action, and pool resources.

To this end, the International HIV Treatment Access Coalition (ITAC) was launched in December 2002. ITAC brings together more than 50 partner organizations including people living with HIV/AIDS and their advocates, non-governmental organizations (NGOs), governments, foundations, the private sector, academic and research institutions, and international organizations. Among these groups is the International Association of Physicians in AIDS Care (IAPAC), which brings to the table the formidable experience and guidance of its international staff and physician and allied health professional membership. Other ITAC partner organizations include the International AIDS Society (IAS), the Global Network of People Living with HIV/AIDS (GNP+), the South African Treatment Action Campaign (TAC), and the United Nations Children's Fund (UNICEF).

The ITAC partners' shared goal is expanded access to HIV treatment for all people living with HIV/AIDS who need it, in line with the goals of the Declaration of Commitment of the United Nations General Assembly Special Session on HIV/AIDS.

ITAC aims to mobilize and augment its partners' efforts to increase affordability, availability and uptake of HIV treatments. The experiences of pilot HIV treatment programs offer valuable lessons for scaling up, but need to be widely disseminated. ITAC will add value to current efforts by serving as a platform for exchanging information and enabling knowledge gained from small programs to be applied across much larger populations. It will also pool and coordinate the technical expertise necessary to make this happen.

The coalition's power lies in the complementary skills and capacities of its partners. Different members will contribute to different elements of the coalition's plan of action. ITAC's priorities include:

- Sharing information about pilot initiatives so that lessons learned can be applied to scale up programs;

- Fostering national and international leadership and advocacy, including maintaining pressure for lower drug prices;
- Helping to galvanize and coordinate donor action to assist governments embarking upon treatment programs;
- Supporting the implementation of national HIV treatment programs, including technical support in planning, procurement of drugs and other commodities, and training;
- Developing human resources and new provider models, including private sector-, NGO-, and peer-based services;
- Monitoring and evaluating programs; in particular determining the impact of treatment on care and prevention, and how treatment will be integrated into, and boost, an overall comprehensive response to HIV/AIDS in resource-limited settings;
- Promoting an operational research agenda to improve HIV/AIDS service delivery systems (public and private), as part of wider efforts to improve overall systems performance; and
- Coordinating quality control including services, drug manufacturing, and provider accreditation.

ITAC is guided by an interim Steering Committee composed of representatives of developing countries, bilateral donors, NGOs, and international organizations. The World Health Organization (WHO) provides the secretariat for the coalition. Of note, ITAC is actively searching for new partners, from both developing and industrialized countries. [*Editor's Note: To learn more, visit www.itacoalition.org.*]

Rather than regarding HIV treatments as an additional burden to health systems and national health budgets, let us instead recognize it as a crucial investment with good economic returns—increasing life expectancy, productivity, and quality of life. HIV treatment stands to serve as a powerful new motor for the overall response to HIV/AIDS, for prevention efforts, indeed, for the long-term sustainability of health systems as a whole. ■

Bernhard Schwartländer is Director of the Department of HIV/AIDS at the World Health Organization in Geneva. Joep MA Lange is President of the International AIDS Society and Chair of the ITAC's interim Steering Committee.

IAPAC commits to 'fast action'...

Continued from page 5

sees a growth to US\$4.5 million, reflects significant expansion of the association's programmatic plans for the upcoming year in each of its advocacy, medical education, and technical assistance missions.

Foremost among those projected efforts are the completion of the GALEN curriculum material and certification process by early 2003; increased recruitment and retention of IAPAC members, with a focus upon expanding member services globally; the significant expansion of IAPAC's Southern Africa Regional Office (IAPAC-SARO) including its formidable role as training provider for Pfizer's Diflucan Partnership Program in 23 African countries; vitalization of IAPAC's European Regional Office (IAPAC-EURO) in Paris; increased physician and patient HIV care tools; and an increase in the scope of clinical and policy review provided through the *IAPAC Monthly* and *JIAPAC*.

"As IAPAC enters into 2003, it is critical that we not rest content with what has thus far been accomplished," stated Zuniga. "Since the IAPAC Board of Trustees has entrusted me with the continued responsibility for leading the association through its next period of growth, I have stressed to IAPAC staff and partners the need to recommit to 'fast action' in the face of human devastation wrought by HIV/AIDS."

According to Zuniga, critical to IAPAC's success is the need to limit bureaucracy and administrative overhead; to share, promote, and build on best practices; to act as a portal for knowledge on HIV care and support; and to transition from traditional, exclusively clinical responses to HIV disease to more conscientious responses based on a public health approach.

These guiding principles of sound organizational management and ethical program design and implementation were described by Zuniga as those to which the success of IAPAC in more recent years is directly attributable, as well as those alone by which the global community of people living with and affected by HIV/AIDS will be able to sustain hope for an end to preventable suffering and death. ■

Scott A. Wolfe is Director of Communications & International Relations at the International Association of Physicians in AIDS Care (IAPAC) Headquarters in Chicago.

A large industrial crane structure, possibly a derrick or tower, is silhouetted against a dramatic sunset sky. The sky transitions from a deep blue at the top to a bright orange and yellow near the horizon. The crane's lattice structure is clearly visible, and it appears to be lifting a large, dark, rectangular object. The foreground is dark and indistinct.

Heavy lifting in Glasgow

(wherein HIV
researchers
uncrate some
Clydeside
surprises)

Mark Mascolini

Glasgow, deep in drear November, can hold bright surprises. Clinicians attending the Sixth International Congress on Drug Therapy in HIV Infection—"the Glasgow meeting"—got more than a few. For starters:

- One morning, they saw the sun.
- One evening, they saw the moon.
- One afternoon, they learned that Glaxo reps, innocently selling zidovudine (AZT), may be selling stavudine (d4T) as well.

That last nugget surfaced in Glasgow's pharmacology session when French researcher Jacques Grassi stunned the uninitiated and the initiated as well with evidence that some AZT turns into d4T inside people's cells—maybe enough to have clinical consequences (see the next section). His results—already stirring debate, speculation, and more study—surely require confirmation. But, if verified, they demonstrate again how outrageously ironic, confounding, and unpredictable HIV medicine can be.

A stock line in reports on recent HIV meetings is that they lack "breakthrough news." But it's not true. Breakthroughs happen all the time. It's just that reporters and reviewers got blinded by the incandescent dawn of potent combinations that turned HIV infection into a 30 Years' War against drug toxicity instead of a fast, messy battle against invincible opportunists. No, the breakthroughs are still there, even if they fail to announce themselves in neon. To find them, one need only track the literature, follow the meeting news, and connect the dots.

Glasgow—coming after headline-siphoning summer and fall meetings—can offer the ideal forum for linking some data dots and seeing whether what emerges makes sense. Grassi's little shocker is only the most obvious example. Sparks arcing from his serendipitous *trouvaille* may illuminate still-dark corners of mitochondrial toxicity and nucleoside (NRTI) cross-

resistance. For example, David Nolan, who closely studies mitochondrial mischief in Simon Mallal's Perth group,^{1,2} told *IAPAC Monthly* that, "for me, this may be a crucial piece of the puzzle."

Yet other Glasgow reports extended the research skein with less startling—though already less tenuous—threads:

- Three other pharmacology studies established the greater tolerability of lower-dose indinavir/ritonavir for first-line therapy (but at some risk).
- Several reports cataloged the rock-ribbed durability of potent regimens in clinical practice.
- Three studies clarified the consequences of treatment interruptions (TIs) and added to the TI risk profile outlined in recent publications.
- Fresh appraisals of adherence sharpened the focus on this *sine qua non* of treatment success.

Can these advances be labeled "breakthroughs"? One could argue yes. For someone who has kept HIV under wraps with indinavir/ritonavir—at the cost of sore sides and cracked lips—a lower yet still effective dose allows a breakthrough to an easier life and fewer temptations to skip a dose. For someone toying with trying treatment breaks, a physician dispensing hard data can break through the web of hypotheses and prevent irremediable mistakes. For someone who got the adherence lecture—once, a while ago—new insights on making adherence routine (plus smaller, fewer, friendlier pills) can make antiretrovirals work more than a year or two.

"Breakthroughs" like these don't make headlines. Sometimes they don't even get noticed. And they all require heavy lifting—by the people who make the pills, the people who take the pills, and the people who do the research to make the taking simultaneously easier and more effective. Everyone who walked or rode to the Glasgow meeting hall each penumbral November morn got a daily reminder of heavy lifting. A mere parking lot away from the Scottish Exhibition and

Conference Center stands the hulking Clydeport crane (left), greeting the surprising prospect of a wintry sunrise, but ready for work in weather good and bad.

PKs AND TREATMENT PLANS

Before they're even ready to perform, nucleosides must jump through three hoops. With the first leap they shed their native garb and assume a monophosphate mantle. With the second vault they don diphosphate dress. With the final bound they emerge in triphosphate finery, ready to masquerade as native nucleotides and ruin HIV's transcription theatrics. The nucleoside d4T executes this triple leap with aplomb, as the lion's share of native drug gets converted into d4T triphosphate (d4T-TP). But AZT stumbles at the very first hoop, and by the time it trips through the third ring, only about 7 percent of the native drug has changed into triphosphate togs.²

Because of this poor conversion—or phosphorylation—to its triphosphate form, and for other reasons, Perth researcher David Nolan told *IAPAC Monthly*, "I have always had trouble coming to grips with the mechanism by which AZT leads to [mitochondrial DNA] depletion," the proposed mechanism of mitochondrial toxicity. Work by Jacques Grassi (CEA, Gif-sur-Yvette) may help Nolan get a better grip.

Conjuring d4T from AZT (philosopher's stone not required)

Working on an assay that may allow simultaneous detection of nucleoside triphosphates (see note 3), Grassi and colleagues at the University Hospital of Bicêtre were busy looking for d4T-negative controls. Their strategy seemed logical enough: measure triphosphates in peripheral blood mononuclear cells (PBMCs) of people taking NRTIs other than d4T. To their surprise, the assay spotted d4T-TP in PBMCs from two people taking AZT, but not d4T [abstract PL8.3*].

*Abstracts from the Glasgow meeting are online at <http://www.hiv6.com>.

Running the assay in 15 people taking AZT, they could not detect d4T-TP in five of them. But in the other 10 d4T-TP concentrations ranged from 3.0 to 10.4 fmol per 1 million PBMCs. Those levels represented 4.5 percent to 17.1 percent of the AZT-TP measured. The median d4T-TP:AZT-TP ratio stood at 12.6 percent in these 10 people. The assay never found d4T-TP in cells from people not taking AZT or d4T. Do these petite d4T-TP footprints fit into the triphosphate tracks laid down by d4T itself? Not quite, but maybe enough to matter. Comparing d4T-TP levels in people taking AZT and people taking d4T in another study,⁴ Grassi showed that levels in AZT takers lie in the lower range of concentrations found in d4T takers.

The bigger question is whether this new assay³ can be trusted. The University of Liverpool's David Back told *IAPAC Monthly* that Grassi's "methodology seems to be very sound," though Back can't figure where the d4T-TP came from. He suspects it may be a breakdown product of AZT-TP rather than a result of AZT phosphorylation. Whether this d4T-TP residue has some clinical impact, Back believes, depends on the relative concentrations of the two triphosphates and on their relative affinity for reverse transcriptase. Back is collecting the data he needs to suggest an answer.

Nijmegen pharmacologist David Burger (University Medical Center St. Radboud) proposed several grounds for caution in interpreting Grassi's results. First, he wrote to *IAPAC Monthly*, "the technique of measuring triphosphates is extremely difficult. Therefore, such techniques are highly prone to errors in outcomes." Second, Grassi's findings come from only 10 people, so no one can say now whether the results apply to everyone taking AZT. Third, there is no external quality control for Grassi's assay. Without such a control, the results are a matter of "believe-it-or-not."

But if Grassi is right, his findings could throw new light on two nagging issues surrounding AZT and d4T—mitochondrial toxicity and cross-resistance. David Nolan explained to *IAPAC Monthly* that his difficulty in "coming to grips" with how AZT depletes mitochondrial DNA (mtDNA) rests on two concerns: "All of the literature, based on *in vitro* data, suggests that (1) AZT is a poor inhibitor of polymerase-gamma [which mediates synthesis and

repair of mtDNA] and (2) not much free AZT gets converted to active AZT-TP (about 7 percent), because it gets 'stuck' at the AZT-monophosphate stage" (see reference 2). Because d4T has *high* affinity for polymerase-gamma, the production of d4T-TP in cells exposed to AZT "may provide a very neat explanation for the mtDNA-depleting effects of AZT."

What could be the clinical fallout of these mitochondrial machinations? It's easy to imagine at least one. Three studies show that replacing d4T with AZT slowly reverses peripheral fat atrophy,⁵⁻⁷ a purported mitochondrial toxicity. Could concentrations of d4T-TP in people switched to AZT be too low to worsen atrophy, but just enough to slow its reversal to a crawl? "This must be a possibility," David Back allows. Whether traces of d4T-TP in blood cells of people taking AZT contribute to the demonstrated cross-resistance between these thymidine analogs remains even more speculative, but people are thinking about it.

One 10-minute slide talk cannot, in a stroke, solve long-standing riddles of resistance and toxicity. But it can at least suggest that some riddles are soluble. And while Grassi's fresh clues inspire keen researchers like Back and Nolan to approach the sphinx anew, no one should forget that early clues can prove treacherous if interpreted too glibly. A famous example of over-hasty conclusions, David Burger reminded *IAPAC Monthly*, involved—yes—d4T-TP. One study suggesting slower d4T metabolism in people with AZT experience⁸ launched a heated campaign to prescribe d4T first. That campaign cooled down fast, though, when a second study⁹ failed to confirm the first.

Indinavir/ritonavir: How low can you go?

A smaller pharmacokinetic surprise surfaced in Glasgow—three tries at testing the toxicity-sparing potential of indinavir and ritonavir at 400/100 mg twice daily. In the two studies that involved treatment-naïve people, low-dose indinavir controlled viral replication well and etched a friendlier side effects profile than the more familiar 800/100 mg twice daily. But one of these studies and a crossover trial in healthy volunteers bared the risk of perilous indinavir troughs with the low dose.

Jürgen Rockstroh (University of Bonn, Germany) outlined his approach to indinavir/ritonavir dosing in a satellite symposium

and backed it up with a randomized, crossover study of 600/100 versus 400/100 mg twice daily in 16 healthy volunteers [abstract P182]. Except in people coinfecting with hepatitis B or C virus, he typically begins with an 800/100-mg dose and doesn't bother with drug level monitoring. But if indinavir toxicity starts taking a toll, Rockstroh trims the dose to 600/100 or 400/100 mg, now checking indinavir levels to ensure adequate troughs.

The crossover study enrolled nine men and seven women who took 600/100 mg or 400/100 mg twice a day for two weeks before 12-hour sampling for drug levels. Then they switched to the other dose for two weeks. Geometric mean minimum concentrations, maximum concentrations, and total exposure proved significantly lower during 400-mg dosing (Table 1). While taking 600 mg of indinavir, no one had a trough below the recommended threshold of 0.10 mg/L. But three people saw their troughs slip below that mark while taking the 400-mg dose, a finding that underscores the need for therapeutic drug monitoring with this dose.

The lower indinavir dose caused substantially fewer side effects in this short study. While taking 600 mg four people had dysuria and one had to stop the protease inhibitors (PIs) because of flank pain. Two people complained of dysuria while taking 400 mg, and none had to stop the drugs. Crystalluria proved equally common with both doses. Other familiar indinavir or ritonavir side effects—gastrointestinal (GI) gripes, dry skin or lips, paresthesias—proved more severe with the higher dose. Fasting triglycerides and total cholesterol rose smartly with either dose. Overall, average triglycerides climbed from 88 to 139 mg/dL and cholesterol from 187 to 228 mg/dL.

A 24-week study of 16 men and 14 women beginning antiretroviral therapy with 400/100 mg of indinavir/ritonavir twice daily charted good RNA and CD4⁺ responses [abstract P18]. But Claudine Duvivier and colleagues at two Paris hospitals found that indinavir lite did not always go down easy and that indinavir troughs dropped as follow-up continued.

The cohort included 20 Caucasians, 17 people from northern Africa, and three from sub-Saharan Africa. They had a worrisome median CD4⁺ count of 84 cells/mm³ (range 3 to 558 cells/mm³) and a lofty median viral load of 230,975

Table 1. **Indinavir exposure (with 100 mg ritonavir) in 16 healthy volunteers**

	600 mg	400 mg	Ratio	P
Mean C _{min} (mg/L)	0.49	0.19	0.38	<0.001
Mean C _{max} (mg/L)	6.03	3.84	0.63	<0.001
Mean AUC (h • mg/L)	30.15	16.18	0.55	<0.001

C_{min} = minimum concentration; C_{max} = maximum concentration; AUC = area under the concentration-time curve.

Source: J-C Wasmuth, abstract P182.

copies/mL (range 5,000 to 750,000 copies/mL). Six people (15 percent) had to quit treatment before week 24 because of side effects, and two others (5 percent) stopped keeping appointments. Grade 3 or 4 side effects included GI problems and diabetes (in two each) and xerosis, arthralgias, “renal toxicity,” and hemolysis in one each.

While the median CD4⁺ count climbed from 84 to 188 cells/mm³ through 24 weeks, the median viral load fell from 5.36 to 2.28 logs (about 229,000 to 190 copies/mL). By intent-to-treat analysis, 27 of 40 people (67.5 percent) had a viral load below 400 copies/mL at week 24. The 24-week on-treatment sub-400 rate measured 87 percent. The only resistance mutation that arose when treatment failed was the lamivudine (3TC)-linked M184V change.

Again this study showed that low-dose indinavir/ritonavir requires routine drug level checks, at least in the early months. Whereas 31 of 34 people (91 percent) assessed at week 4 had an indinavir trough above a threshold of 150 ng/mL, by week 24 only 13 of 19 (68 percent) still had an adequate trough.

Clinicians from Saint-Pierre University Hospital in Brussels offered the biggest study of low-dose indinavir/ritonavir in a nonrandomized, prospective analysis of 181 people starting twice-daily antiretrovirals [abstract P16]. D. Konopnicki and colleagues compared 71 people starting nelfinavir, 56 starting 800/100 mg of indinavir/ritonavir, and 54 starting the PIs at 400/100 mg. The three groups matched well in median age (34, 34, and 33.5 years), viral load (4.84, 5.02, and 5.02 logs), and CD4⁺ count (193, 207, and 250 cells/mm³).

Intent-to-treat and on-treatment analyses discerned no significant differences between the groups in 48-week CD4⁺ gains or proportions with a viral load under 50 copies/mL. But when it came to tolerability, the 800/100-mg group significantly lagged those taking nelfinavir or 400/100 mg of the PIs. After 48 weeks 61 percent had

stopped 800/100 mg of indinavir/ritonavir because of side effects compared with 15 percent in the 400/100-mg group and 6 percent in the nelfinavir group (*P* < 0.001). The probability of treatment interruption proved significantly higher in the high-dose double PI group than in the other groups at 12, 24, and 48 weeks (*P* < 0.0001). While 37 people (66 percent) who started 800/100 mg of indinavir/ritonavir had at least one treatment-related side effect and 12 (21 percent) had two or more, 13 (24 percent) starting 400/100 mg had at least one side effect (*P* < 0.0001) and four (7 percent) had two or more (*P* = 0.06). Among 21 people who switched from 800/100 mg to 400/100 mg because of toxicity, side effects resolved or improved in 17 (81 percent).

Week 4 drug level monitoring found dangerously low indinavir troughs (<150 ng/mL) in only three of 30 (10 percent) taking 400/100 mg of indinavir/ritonavir, including one trough below 80 ng/mL. Among seven people taking 800/100 mg who had drug levels checked at week 4, two (28 percent) had a trough under 80 ng/mL. But everyone with low indinavir troughs had a viral load under 50 copies/mL. It would be interesting to see if more 24-week troughs sagged in this cohort, as they did in the French study. The higher proportion of low indinavir levels with 800/100 mg may reflect toxicity-driven lapses in adherence or the small sample.

A salvage sally with low-dose indinavir

If toxicity limits use of full-dose indinavir in people just starting antiretrovirals, those with dog-eared dossiers of regimen revisions may stand to gain even more from easy-does-it indinavir dosing. That’s why Marianne Harris and Vancouver colleagues looked at 600 instead of 800 mg of indinavir twice daily when given with lopinavir/ritonavir [abstract P170]. The study involved 13 men, four of whom also took saquinavir (800 or 1,000 mg twice

daily), and six of whom added a nonnucleoside to their regimen. Those six took 533/133 mg of lopinavir/ritonavir twice daily, while the others took the standard dose. All but one person took nucleosides.

Measuring drug levels between two and 10 weeks after starting the regimens, Harris charted a median indinavir trough around 400 ng/mL, but the range stretched from 0 to 1,600 ng/mL. Historically, she noted, indinavir troughs average about 900 ng/mL with an 800/100-mg dose. Indinavir peak levels (median 3,200 ng/mL) also stood substantially lower than historical peaks with 800/100 mg (about 7,200 ng/mL). Lopinavir peaks and troughs approximated those recorded when given without other PIs or nonnucleosides.

Among 12 men with presalvage resistance tests, six had protease mutations that translated into a 19-fold change in indinavir 50 percent inhibitory concentration (IC₅₀) compared with wild-type virus, a 37-fold lopinavir change, and a 22-fold saquinavir change. One of these six had nearly a 4-log climb in viral load after two weeks of salvage, but the other five had a median 4.4-log drop after a median 4 weeks. Among six people without protease mutations at baseline, viral loads dropped a median 4.8 logs after 4.5 weeks.

Harris reported that the salvage regimens were “well tolerated” by everyone, but she did not offer specifics.

From nonnukes to no nukes

The history of salvage therapy began with a nonnucleoside replacing or abetting protease inhibitors. But the newest salvage sortie employs a *no-nuke* strategy meant to ease mitochondrial toxicities or to avoid drugs already hamstrung by cross-class resistance. In a satellite symposium, David Cooper (University of New South Wales, Sydney) suggested four groups who may be candidates for NRTI holidays:

- People who began treatment with a double-NRTI combo
- People with multiple thymidine analog mutations* (TAMs) or multinucleoside-resistant virus
- People in whom a triple-nucleoside regimen failed
- People with serious nucleoside toxicity

*Mutations shared by the thymidine analogs AZT and d4T are M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E.

And what nuke-sparing regimens merit study? Cooper had these suggestions:

- PIs plus a nonnucleoside
- A fusion or entry inhibitor (when available) plus PIs
- A ritonavir-boosted PI

Wait a minute. A PI-*only* regimen? Didn't that tactic come up short in the sobering induction-maintenance trials of yesteryear? Yes, but Pietro Vernazza (Cantonal Hospital, St. Gallen, Switzerland) is trying it again and—in a highly selected group—early results are good. Cooper outlined 20-week trends in Vernazza's study of people given 400 to 800 mg of indinavir twice daily plus 100 mg of ritonavir. Everybody had a viral load below 50 copies/mL for at least three months, no one had a virologic failure on their chart, and (to ensure a rescue option) no one had nonnucleoside experience. Vernazza picked indinavir because it penetrates the central nervous system, and he adjusted the dose with drug monitoring. Through week 20 seven of eight people maintained a viral load under 50 copies/mL; the eighth had one blip above 50 copies.

Elke Lauenroth-Mai and colleagues in a Berlin practice took a more complex nonnucleoside route in 18 people—all with PI experience and a median antiretroviral history of 5.9 years [abstract P235]. The Berlin clinicians arched their rescue regimen around a keystone comprising standard-dose lopinavir/ritonavir and 666 mg of indinavir twice daily, reasoning that lopinavir can subdue virus already burdened by multiple protease mutations and that indinavir penetrates sanctuary sites.

Four people without nonnucleoside experience started efavirenz or nevirapine, and eight started the nucleotide analog tenofovir. None starting tenofovir had more than three TAMs (including M41L and L210W) or the multinucleoside-resistant mutation Q151M or T69SS. They began salvage with a median CD4⁺ count of 235 cells/mm³ (range 12 to 543 cells/mm³) and a median viral load of 135,000 copies/mL.

All 18 people completed 24 weeks of treatment with the new regimen, and nine had made it to week 48. The Berlin group quelled GI toxicity in three people by cutting the lopinavir/ritonavir dose to 266/66 mg twice daily. They trimmed the indinavir dose to 400 mg twice daily in two people because of side effects. No one in the study

had indinavir-related renal complaints.

By week 24 the median CD4⁺ count added 175 cells/mm³ (range 117 to 198 cells/mm³). Among those with 48 weeks of follow-up, the median CD4⁺ gain measured 197 cells/mm³. Nine of the 18 had a viral load under 50 copies/mL by week 24, and six of nine had a sub-50 load at week 48.

What separated week 24 responders from nonresponders? Baseline protease mutations proved the clearest discriminator. Among the seven nonresponders who had baseline genotypes, all had more than five PI-puncturing mutations, including L10I, D30N, M46L, I54V, L63P, V82A, and L90M. Among six people who started salvage with lopinavir experience, five fell into the nonresponse group. But among seven with baseline indinavir experience, only three failed to notch a sub-50-copy load at week 24.

Tenofovir added little to the antiviral activity of these regimens. Of the nine people who used the nucleotide, only one had a 24-week viral load under 50 copies/mL. Not surprisingly, starting a nonnucleoside did bolster the regimen. Three of the four people starting their first nonnucleoside were 24-week responders.

Median fasting triglycerides rose 110 mg/dL through week 24, and two of 18 people had a triglyceride level above 500 mg/dL. Total cholesterol rose by a median 67 mg/dL at week 24; protective high-density lipoprotein (HDL) cholesterol accounted for 11.5 mg/dL of that gain. Meanwhile, venous lactates fell by a median 0.41 mmol/L through week 24. Whereas nine people had lactates above 2.2 mmol/L at baseline, only three did at week 24.

Yet mitochondrial-friendly nukeless regimens do not always sit on the stomach as kindly as chamomile tea. Daniela Gey (University of Heidelberg) and colleagues found that nine of 18 people who tested the no-nucleoside waters came away scalded [abstract P122]. All 18 suffered from a mitochondrial toxicity, lipoatrophy, or both when they started saquinavir/ritonavir (1,000/100 mg twice daily) plus standard-dose efavirenz and nevirapine. Their median 3.93-log viral load (about 8,500 copies/mL) stayed stable through 24 weeks, as did their CD4⁺ counts. Median lactates dipped from 1.8 to 1.5 mg/dL.

But the full-dose double NNRTIs probably proved this regimen's undoing. Six people quit treatment because of rash, while nausea or diarrhea forced two more

to stop. Another person dropped out because of the onerous 19-pill regimen. Gey proposed that starting with 600 mg of efavirenz daily for two weeks may improve this regimen's tolerability. But whether double nonnukes ever make sense remains an open question. Gey did not report the treatment experience in these people.

A study of 198 people starting a rescue regimen after AZT or d4T experience bolstered the rationale for more study of NRTI-sparing tactics in people with plentiful thymidine analog mutations [abstract P228]. Mauro Zaccarelli (National Institute for Infectious Diseases "Lazzaro Spallanzani," Rome) tracked people who started new regimens based on genotyping and expert advice in 1999 and 2000. All new combinations included two or three NRTIs.

After a median 60 weeks of follow-up, only 111 (56 percent) had one or more undetectable viral load readings. Beginning the rescue regimen with two TAMs lowered the chance of having an undetectable viral load by 7 percent, and starting with three TAMs lowered the chance by 24 percent. That downtrend became statistically significant only with four or more TAMs, which lowered the chance of a virologic response 65 percent ($P = 0.01$).

Trio or tetra for first-line therapy?

If one counts a ritonavir-boosted PI as a single drug, should therapy start with three antiretrovirals or four? Though some research shows that more drugs control viral replication faster,^{10,11} does that faster action pay clinical dividends? Some suggest that the extra antiviral pop from the fourth drug makes most sense for people with ultralow CD4⁺ counts who need a quick turnaround. And a study by Ed Wilkins (North Manchester General Hospital) and colleagues in London showed good 24-week results with a simple four-drug combo of efavirenz plus Trizivir (AZT, 3TC, and abacavir) [abstract P13].

The treatment-naïve participants in the TETRA study all started with CD4⁺ counts under 200 cells/mm³, and 82 percent had fewer than 100 cells/mm³. The average baseline count measured 66 cells/mm³, and the average viral load 554,548 copies/mL. In an intent-to-treat analysis that included people who switched to nevirapine because of efavirenz side effects but excluded people who withdrew, 53 percent had a 24-week viral load below 50 copies/mL. In a 24-week as-treated analysis,

72 percent were under the 50-copy mark. As Wilkins observed, these proportions are likely to climb as the 48-week study continues. The mean CD4⁺ count rose to 211 cells/mm³ by week 24.

But would these people do as well on three drugs, efavirenz plus Combivir (AZT/3TC), for example? Clinicians as different as Diane Havlir (University of California, San Francisco) and Brian Gazzard (Chelsea and Westminster Hospital, London) think they may. At the 2002 ICAAC Havlir argued that effective therapy depends not so much on the number of drugs in the regimen as on how potent those drugs are.¹² And because four drugs may kick up more toxicity than three, she advised sticking with stalwart triple regimens for now (again counting a boosted PI as one drug).

Gazzard, a coinvestigator in the Wilkins four-drug study, sounded similar cautions in a Glasgow satellite symposium. So far he sees “no evidence at all that we should be using more [than three] drugs.” A Chelsea and Westminster study of Trizivir plus tenofovir left him “impressed by the extra difficulty of taking just one extra—even though ‘tolerable’—drug.”

At least one study bolsters these opinions. ACTG 384 compared two four-drug medleys (efavirenz/nelfinavir plus AZT/3TC or ddI/d4T) with four three-drug combos (efavirenz or nelfinavir plus one or the other NRTI pair) in 980 treatment-naïve people.¹³ After a median 28 months of follow-up, any of the quad therapies halved the time to first regimen failure or first virologic failure when compared with nelfinavir/AZT/3TC, nelfinavir/ddI/d4T, or efavirenz/ddI/d4T. But efavirenz/AZT/3TC was as good as either quad, a result supporting Havlir’s point that potency matters more than mere numbers.

EXPECTING MORE LIFE

Three years ago separate modeling studies at ICAAC and the European meeting in Lisbon predicted that most HIV-infected 40-year-olds taking antiretrovirals could anticipate near-normal life spans.^{14,15} It seems to be coming true. People no longer die of HIV infection, said Bernard Hirschel (University of Geneva) in a Glasgow keynote talk [presentation KL3], at least not if they’ve cleared three iffy hurdles:

- If they didn’t begin treatment before HAART arrived
- If there’s enough time to get them on HAART
- If they have no serious comorbidity (which these days often means liver disease)

Of course that second contingency leaves out most people in Africa, India, China, Russia, and other spots where the epidemic festers. But from the West there are lots of numbers to back Hirschel’s contention. Three Glasgow studies and one anecdotal report documented consistent, balmy trends:

- Growing proportions in clinic cohorts with viral loads under 400 or 50 copies/mL
- An increasingly sustained response to initial regimens
- A dwindling need for resistance testing

Why is this happening? Two obvious reasons: the drugs are better now than in 1996, and clinicians are using them better. Hirschel showed data on regimen preferences across Europe from the first half of 1998 through the first half of 2002. In the first period about half of those studied took HAART version 1.0—two nucleosides and a single PI. Another 20 percent took only two nucleosides, and mere slivers on the histogram reflected nascent use of two nucleosides with a nonnucleoside or with two PIs. A wafer-thin slice augured the dawn of ritonavir boosting.

By the first half of 2000, ritonavir boosting had grown from a wafer to a wedge, while double PI use stayed flat. Double nucleoside therapy shriveled to 5 percent, and two NRTIs plus a PI shrank to 35 percent. In 2000 more than 20 percent of combos relied on a nonnuke. Those trends continued through the first half of 2002, with nonnucleoside regimens accounting for more than 30 percent and single-PI regimens for less than 30 percent. Triple nukes had all but knocked double nukes off the bar chart, and ritonavir-boosted regimens—reflecting the advent of lopinavir—made up about 15 percent of antiretroviral mixes. Throughout the whole period of study, about 20 percent of people took no antiretrovirals.

To Hirschel, these changes say clinicians are tracking the latest studies and—as a result—prescribing more efavirenz and lopinavir. In Switzerland, he added, a study done with the insurance industry

confirmed that people with HIV infection now have the same life expectancy as those without it.

Clinics outshine clinical trials

Much fretting followed early reports of 80 percent response rates with the premier PI regimens, when clinics began reporting that only half their patients cleared virus from blood after starting the magic pill. Some reasons for this dispiriting disparity soon became clear. Many merely added a PI to faltering nucleosides. Many missed the adherence message. Many took hard-gel saquinavir. Many couldn’t stomach ritonavir or indinavir.

Today, Margaret Johnson suggested in a satellite symposium, the tables have turned. People in her clinic at London’s Royal Free Centre for HIV Medicine are doing *better* than cosseted clinical trial enrollees. She reckons that 87 percent of people she sees have a viral load under 400 copies/mL, and 82 percent are under 50 copies. “I think we’re all doing better than we expected based on clinical trials,” she said.

Of course Johnson’s sterling success rate did not emerge from a switch-equals-failure analysis. She counted anyone with fewer than 400 copies as a success, regardless of how many times she tempered or tweaked the regimen. But you don’t find many mopey “noncompleters” with undetectable viral loads. The yearly virologic failure rate in her cohort stands below 4 percent, and case records tie most of those failures to missed pills.

Work by Johnson’s colleague Andrew Phillips shows that the first 24 weeks of treatment are critical to long-term suppression. This study, published just before Glasgow,¹⁶ involved 1,433 people in London and Frankfurt beginning their first HAART regimen and reaching a viral load below 400 copies/mL by week 24; 409 of them had already tried one or two nucleosides. The longer a person’s RNA stayed out of sight, the lower was that person’s chance of a later rebound (Table 2). And that held true regardless of pre-HAART nucleoside experience, although people who took no NRTIs before HAART had consistently lower failure rates. Earlier, Phillips recorded the same fading rebound rate in naïve Frankfurt patients starting HAART.¹⁷

Why does the failure rate shrink to a few percentage points when responders

soldier past their second and third year of treatment? Phillips sees several possibilities, which he divides into a “selection effect” and a latent pool effect. Reason, and clinical experience, suggest that long-term responders are “selected” because they adhere to their regimen, experience little toxicity or tolerate it well, achieve high drug levels, harbor few pretreatment resistance mutations, or “have some other biological advantage.” Alternatively, or additively, ever-ebbing rebounds may reflect an evaporating pool of latently infected cells, though Phillips adds that this pool dries up ever so slowly. Whatever the explanation, Phillips’ exacting analyses of this felicitous phenomenon^{16,17} should be lesson number one in any adherence curriculum.

Long responders replace nonresponders

People in the Royal Free and Frankfurt cohorts aren’t the only ones prospering with improving therapies. At Stockholm’s Huddinge University Hospital, Pehr Olov Pehrson reported that 85 percent of more than 400 people now taking antiretrovirals have a viral load under 50 copies/mL, and 82 percent of them are under 20 copies [abstract P20]. A fair portion of these people, 41 percent, had taken one or two antiretrovirals before starting triple therapy, which the cohort has now taken for a median of 55 months.

Among those ever treated in this group, 80 percent have a viral load under 50 copies/mL, another 8 percent have between 50 and 499 copies/mL, and 5 percent have more than 5,000 copies/mL. CD4⁺ counts top 200 cells/mm³ in 91 percent. In a plenary lecture Anders Sönnberg noted that only 3.5 percent of this cohort got resistance testing in 2002 [presentation PL5.2]. That’s not because Sönnberg has given up on resistance testing; it’s because regimens are failing so rarely.

Things aren’t much worse over at Helsinki University Hospital, according to Matti Ristola [abstract P51]. In a clinic population of about 200 people taking three or more antiretrovirals, 71 percent had a viral load under 400 copies/mL in 1998, a rate that improved to 72 percent in 1999, 80 percent in 2000, and 87 percent in 2001. In 2000 and 2001, 72 percent and 78 percent had viral loads under 50 copies/mL. In 2001, 69 percent were on triple therapy, 26 percent on quad therapy, and 4 percent on five or six drugs.

At the Southern Alberta HIV Clinic in

Table 2. Failure rate fades with longer viral suppression

Treatment experience (n)	After week 24 suppression, viral load below 400 copies/mL for:			
	<1 year	1 to 2 years	2 to 3 years	≥3 years
Naive (1024)	11%	5%	3%	3%
NRTI experienced (409)	40%	11%	11%	5%

Source: Andrew Phillips, reference 16.

Calgary, reported Nikola Ostrop-Hanhoff, more and more people are sticking with their first regimen as the HAART era matures [abstract P17]. The proportion of infected people starting therapy has also dropped consistently (from 96 percent in 1996 to 56 percent in 2001), and they’re starting at lower T-cell counts (293 cells/mm³ in 1996 and 180 cells/mm³ in 2001).

Sustainability, defined as the percentage staying on their first regimen, has climbed steadily over the years, a gain that Ostrop-Hanhoff attributed partly to efavirenz. She found that 57 percent starting a nonnucleoside (97 percent efavirenz) and 55 percent starting a PI (65 percent indinavir) kept the same regimen for 12 months. But by month 30 only 25 percent had stuck with their PI regimen versus 55 percent in the NNRTI group. In 1996 first-regimen sustainability measured 69 percent at month 6, 39 percent at month 18, and 23 percent at month 24. By 2000 those rates had improved to 67 percent, 62 percent, and 62 percent.

Six-month and one-year start signals

The greater durability and tolerability of more recent regimens beg the question whether clinicians should reconsider starting treatment at higher CD4⁺ counts and lower viral loads. If the big arguments against starting earlier are the risks of toxicity and virologic breakthrough, today’s more people-friendly and resistance-resistant regimens seem to cry for quicker use.

But the critical question about starting therapy, Andrew Phillips proposed in Glasgow, remains whether faster treatment wards off AIDS or death better than beginning later [presentation PL1.1]. To address that question he weighed three variables—age, CD4⁺ count, and viral load—on an unusual endpoint: risk of AIDS or death after six months. He argued that these short-term termini make more sense than AIDS or death at two or three years, because most people diagnosed with HIV infection get a checkup every three

to six months. And clinicians are more concerned about what may happen before they next see an untreated person than about what may happen three years hence.

The CASCADE cohort that Phillips analyzed included more than 3,000 people with known CD4⁺ and RNA tallies before starting antiretrovirals. For a 25-year-old with a viral load of 10,000 copies/mL and a CD4⁺ count of 200 cells/mm³, the six-month risks of AIDS and death measured only 2.3 percent and 0.3 percent. For 45-year-olds with the same numbers, respective risks measured 3.6 percent and 0.6 percent. Those risks approximately doubled for people in both age groups with a viral load of 100,000 copies/mL.

Six-month risks of AIDS or death were lower, but not zero, at CD4⁺ counts of 350 cells/mm³, for both age groups and both viral load brackets. For example, 45-year-olds with a six-figure viral load and 350 cells/mm³ had a 2.9 percent risk of AIDS in six months and a 0.6 percent risk of death.

Are such risk levels, even though small, high enough to justify the risks of antiretroviral therapy? “If the dominant concern is to avoid AIDS and death over the next few years,” Phillips counseled, “the better strategy is to start therapy immediately.” But the risk of AIDS is low and the risk of death lower still, even with deferred therapy. On top of that, if an untreated person has 350 CD4⁺ cells/mm³ today, that person probably won’t approach 200 cells/mm³ until 2007. By then antiretrovirals will be even more potent and tolerable, and clinicians will know more about monitoring patients and promoting adherence. So a person who defers therapy today—and *survives* until 2007—may stand a better chance of long-term health than the person who starts antiretrovirals now.

Another way to frame an answer, Phillips offered, is to look at risk cutoffs for other diseases. For example, 1998 British guidelines call for antilipid medications in people with at least a 1.8 percent six-month risk of coronary heart disease.

If HIV clinicians applied that benchmark to AIDS, they would start antiretrovirals for both 25-year-olds and 45-year-olds with 350 cells/mm³ and viral loads of 100,000 copies/mL—though not for either age group with 350 cells/mm³ and a viral load of 10,000 copies/mL. But such analogies are loose, Phillips cautioned, because today's antiretrovirals are more toxic than lipid lowerers.

Multicenter AIDS Cohort Study (MACS) researchers published a similar exercise shortly after Glasgow, looking at one-, two-, and three-year risks of AIDS or sub-200 CD4⁺ counts in 1,504 untreated gay men who enrolled in the cohort from 1985 to 1988.¹⁸ Among 231 men who came into MACS with 200 to 350 cells/mm³, none with fewer than 10,000 RNA copies/mL had an AIDS-defining disease or a CD4⁺ count under 200 cells/mm³ within one year. For those in this CD4⁺ bracket who started follow-up with 10,001 to 20,000 copies/mL, none had clinical AIDS and 8 percent had a sub-200 CD4⁺ count within a year. But people with viral loads under 20,000 copies/mL made up only 29 percent of the 200- to 350-CD4⁺ contingent.

For 1,273 MACS members who enrolled with more than 350 cells/mm³, the critical RNA cutoff was 60,000 copies/mL. No one with more than 350 cells/mm³ and a viral load under 60,000 copies/mL (79 percent of the group) had an AIDS diagnosis in one year, although 11 percent in the 40,000 to 50,000 RNA bracket and 8 percent in the 50,000 to 60,000 bracket had fewer than 200 CD4⁺ cells/mm³ in one year.

The MACS team concludes that their findings support current US guidelines on starting antiretrovirals, and they propose a decision tree for starting treatment in people without AIDS:

- If the CD4⁺ count lies below 200 cells/mm³, start.
- If the CD4⁺ count lies between 200 and 350 cells/mm³:
 - Start if the viral load lies above 20,000 copies/mL.
 - Defer if the viral load lies below 20,000 copies/mL.
- If the CD4⁺ count lies above 350 cells/mm³:
 - Start if the viral load lies above 60,000 copies/mL.
 - Defer if the viral load lies below 60,000 copies/mL.

Table 3. How the Case Definition Study and FRAM differed

	Case Definition Study	FRAM
Goal	Provide a case definition for use in research	Describe phenotype and estimate prevalence
Assumptions	Assumed phenotype	Did not assume phenotype
Case-control comparison	Correlates of clinical cases compared with HIV-infected controls without phenotype	Correlates in randomly selected HIV-infected cases compared with healthy controls

Source: William Powderly, presentation PL9.5.

EXPECTING A HARD LIFE

The European AIDS Treatment Group's Arjen Broekhuizen, reflecting on the promise that HAART would let people with HIV lead normal lives, proposed instead that HAART lets one "live a hard life." Two of the hardest parts are side effects that advertise one's serostatus—the fat deformities of lipodystrophy—and those that threaten a shorter life with a faulty heart. Both topics got their due in Glasgow.

FRAMING a lipodystrophy definition

Although few new morphologic or metabolic findings emerged in Glasgow, meeting organizers invited the top investigators of the Lipodystrophy Case Definition Study (Andrew Carr, St. Vincent's Hospital, Sydney) and the Fat Redistribution and Metabolic Change in HIV (FRAM) Study (Carl Grunfeld, University of California, San Francisco) to air their sometimes antipodal findings side-by-side. They also prevailed on William Powderly (Washington University, St. Louis), the only researcher who worked on both studies, to referee [presentation PL9.5].

An online review¹⁹ spells out details of the Case Definition Study and preliminary results from FRAM. Both studies see lipoatrophy as a hallmark fat failure in people with HIV infection. According to the Case Definition, central fat buildups distinguish people with lipodystrophy from HIV-infected people without the syndrome. But FRAM found that neither central fat gain nor buffalo hump separated men with HIV from age-matched seronegative controls. (FRAM data on women remain under wraps.)

Why the difference? The two studies' divergent goals and methods explain much, Powderly proposed. Although both made cross-sectional comparisons, the comparison groups and baseline assumptions

differed (Table 3). Both studies, Powderly noted, have their limits. Because both are cross-sectional, neither can gauge progression of fat abnormalities. Also, the Case Definition Study does not address degrees of lipodystrophy and may underestimate or miss milder expressions of the syndrome. The Case Definition Study began with a subjective identification of cases and controls—based on an assumption of the syndrome's main features—so it may suffer from selection bias.

FRAM's main limit may be the relevance of the control group, according to Powderly. Although the population selected—people in the CARDIA heart disease cohort—reflect the tendency to overweight in the US population, that does not necessarily make CARDIA the best control group for learning lessons about lipodystrophy. FRAM doesn't address the hypothesis that untreated HIV-infected people have scanty visceral adipose tissue that grows with therapy—because 95 percent of FRAM cases took antiretrovirals.

Powderly suggested that criteria used to define buffalo hump in FRAM may explain the similar rates of that fat buildup in cases and controls. He also stressed, as Carl Grunfeld has, that FRAM does *not* say that people with HIV don't have excess visceral fat. Instead it shows that, compared with CARDIA controls, visceral adiposity is not more common in people with HIV infection and is not statistically linked to lipoatrophy.

FRAM's most important lesson, Powderly believes, is that lipoatrophy is more common than anyone thought in people with HIV infection. But he cautioned that *when* you measure fat atrophy can make a big difference in a cross-sectional study. Two recent trials show that limb fat *increases* during the first few months of antiretroviral therapy, then begins to wane.^{20,21} Measuring arm and leg fat in people who started antiretrovirals eight

weeks ago will paint a plumper picture than measuring limb fat in people treated for three years.

Grunfeld's key conclusion from FRAM—a conclusion credited by experts including Powderly—is that lipoatrophy and lipohypertrophy are separate syndromes and should not be lumped into a single “lipodystrophy” syndrome.

Whatever the merits and demerits of these two studies, the ultimate arbiter of their worth will not be William Powderly or any other analyst. HIV docs will decide whether either offers a clinical edge, or at least a sharper sense of what lipodystrophy (or lipoatrophy and lipohypertrophy) mean. By the time of the Glasgow meeting, Carl Grunfeld had laid out results from some of the men, and none of the women, enrolled in FRAM. Even when the first complete data set appears, this rich trove of evidence will require more time for full analysis.

Clinicians won't have to wait as long to size up the Case Definition Study. Andrew Carr has already put it in publication shape, and it should appear in a refereed journal around the same time as this article. When it does, Carr and colleagues will also post several online interactive calculators (<http://www.med.unsw.edu.au/nchecr>) that will allow clinicians with varying sets of clinical, laboratory, and body scan data to see if the Case Definition makes sense for them.

Lessons on lipids and lesions

Two studies presented in Glasgow—one big, one small—detailed the varying risks of high lipids, vascular lesions, and myocardial infarctions (MIs) in people taking different antiretrovirals. But a third study underlined an already-italicized theme of several heart risk studies: Many HIV-infected people have plenty of worrisome *nondrug* risk factors.

Surveying 394 outpatients (including 334 men) at London's Royal Free Hospital, Collette Smith [abstract P156] found that the most consistent risk factors had nothing to do with HIV infection:

- Cigarette smoking (45 percent)
- Older age (34 percent older than 40 years)
- Family history of heart disease (29 percent)
- Overweight (20 percent with a body mass index above 26 kg/m²)
- Excess alcohol consumption (7 percent)

The risk picture grew scarier still in people taking HAART. Compared with those not on HAART, higher proportions of HAART-treated people had a total cholesterol above 6.3 mmol/L (23 versus 0 percent), triglycerides above 2.9 mmol/L (43 versus 4 percent), HDL cholesterol below 0.9 mmol/L (11 versus 6 percent), high blood pressure (12 versus 10 percent), and diabetes mellitus (3 versus 0 percent). But fewer HAART takers were older than 40 (40 versus 89 percent), smoked (43 versus 47 percent), or drank alcohol above “recommended limits” (6 versus 10 percent). The survey also suggested one hidden benefit of starting HAART: Although 72 percent of this cohort's smokers had tried and failed to quit, 65 percent of ex-smokers stopped when they started HAART.

What type of HAART one takes matters in MI risk calculations, according to a multicohort D:A:D* analysis presented by Jens Lundgren (University of Copenhagen) [abstract PL9.2]. Applying the Framingham risk equation to 13,326 men and 4,278 women with HIV infection, he found a consistently low three-year MI risk among women (0.1 percent or lower) regardless of treatment experience or current therapy. But for men the three-year risk clambered from 0.4 percent in the treatment naive, to 0.7 percent among those taking only nucleosides, to 0.9 percent among those taking a nonnucleoside, to more than 1 percent among those on a PI, and to more than 1.2 percent for those taking both a PI and an NNRTI.

Which PI or PIs one takes also alter the risk equation, according to another D:A:D analysis presented by Christian Pradier of Nice [abstract PL12.1]. Ritonavir had the worst lipid scores and nelfinavir the best in this analysis of 7,729 people (79 percent men) taking licensed PIs but not nonnucleosides. The study did not pin down lipid numbers in people taking lopinavir, which got grouped with other ritonavir-boosted PIs. A multivariate analysis adjusted for age, gender, cardiovascular risk factors, CD4⁺ count, viral load, current nucleosides, previous nonnucleosides, treatment experience when starting a PI, and year of HIV infection yielded the following findings:

*D:A:D stands for Data Collection on Adverse Events of Anti-HIV Drugs.

- Ritonavir doubled the risk of a total cholesterol at or above 6.2 mmol/L (odds ratio [OR] 1.99, $P = 0.0001$), and two PIs including ritonavir raised the risk 2.13 times ($P = 0.0001$).
- Nelfinavir boosted the risk of a high total cholesterol by 28 percent ($P = 0.008$), but that rate reflected good levels of wholesome HDL cholesterol. Nelfinavir cut the risk of a dangerously low HDL cholesterol (≤ 0.9 mmol/L) by 40 percent ($P = 0.0001$).
- Nelfinavir also lowered the risk of a total cholesterol-to-HDL ratio at or above 6.5 by 20 percent, but that drop fell shy of statistical significance ($P = 0.08$).
- Saquinavir nearly halved the risk of a high total-to-HDL ratio (OR 0.52, $P = 0.02$), but that advantage may partly reflect low saquinavir levels in cohort members taking the old hard-gel capsule. D:A:D cohort members took both the old and new saquinavir caps, but Pradier did not have an exact breakdown.
- Ritonavir raised the risk of a high total-to-HDL ratio 48 percent ($P = 0.04$), and a double PI including ritonavir raised that risk 42 percent ($P = 0.02$).
- Ritonavir more than tripled the risk of a triglyceride tally at or above 2.3 mmol/L (OR 3.22, $P = 0.0001$), and a double PI with ritonavir raised that risk 95 percent ($P = 0.0001$).

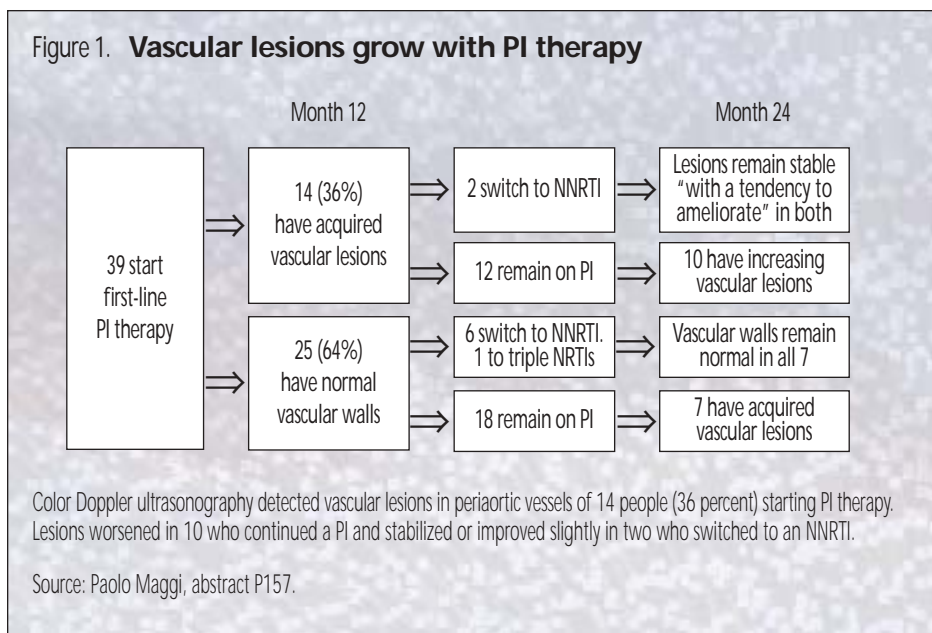
The D:A:D team plans to report cardiovascular endpoints in cohort members next year.

Paolo Maggi (University of Bari) charted progression of vascular wall lesions in vessels near the aorta in a longitudinal study of 39 people starting a first-line PI [abstract P157]. Two people who switched from a PI to an NNRTI had stabilization or possible reversal of lesions. Maggi used color Doppler ultrasonography to check periaortic vessels 12 months after people started taking PIs and 12 months after the first scan (but unfortunately not before therapy). Figure 1 outlines scan results at 12 and 24 months. Maggi linked cigarette smoking, high triglycerides, and CDC disease stage with a higher risk of lesions, but he tied the highest risk to PI therapy. The poster did not spell out these statistical analyses.

How well do statins stanch lipids?

Three studies looked at a statin or a fibrate in people with antiretroviral-induced

Figure 1. **Vascular lesions grow with PI therapy**



hyperlipidemia; two of them (including the largest) showed incomplete responses to the lipid lowerers. Nicholas Smith (Chelsea and Westminster Hospital, London) offered a retrospective analysis of 102 people taking atorvastatin and 77 taking pravastatin [abstract P133]. In this largely (92 percent) gay cohort, total cholesterol fell in 89 percent but returned to a target below 6.5 mmol/L in only 44 percent. More people taking atorvastatin (median dose 10 mg daily) than pravastatin (median dose 40 mg daily) reached the target cholesterol reading. But the pravastatin group started with more cholesterol:

For pravastatin (n = 77)

- Prestatin cholesterol: 8.3 mmol/L with PIs and 7.9 mmol/L with non-PI therapy
- Poststatin cholesterol: 6.8 mmol/L with PIs and 6.7 mmol/L with non-PI therapy
- Percent <6.5 mmol/L: 29 with PIs and 37 with non-PI therapy
- Median statin duration: 45 weeks

For atorvastatin (n = 102)

- Prestatin cholesterol: 7.7 mmol/L with PIs and 7.5 mmol/L with non-PI therapy
- Poststatin cholesterol: 6.3 mmol/L with PIs and 6.2 mmol/L with non-PI therapy
- Percent <6.5 mmol/L: 57 with PIs and 50 with non-PI therapy
- Median statin duration: 33 weeks

Smith recorded no serious statin side effects.

In 20 consecutive patients who started atorvastatin with an LDL above 160 mg/dL, Rosario Palacios (Hospital Virgen

de la Victoria, Málaga) found that the average reading fell significantly and into the reference range, from 203.8 to 127.5 mg/dL ($P < 0.0001$) [abstract P141]. The study involved 16 men and four women who had normal lipids before starting HAART and who did not respond to diet and exercise. Their average age was 47 years, nine had an AIDS diagnosis, 10 smoked, and five were obese. After 24 weeks of atorvastatin at 10 mg daily, total cholesterol and triglyceride averages returned to “borderline high” or normal in this group (Table 4).

For 19 men and one woman with high triglycerides that did not respond to diet or exercise, Palacios tried 200 mg of fenofibrate daily for 24 weeks [abstract P140]. This group’s age averaged 40.5 years, 10 had AIDS, 10 smoked, and three were obese. Again average total cholesterol retreated to the “borderline high” range (Table 4). Triglycerides dropped significantly but remained well above normal. Neither atorvastatin nor fenofibrate affected CD4⁺ counts or viral loads in these people.

CD4 AND RNA SWAY TIs

Two articles published just before Glasgow added to the literature questioning the immunologic rationale for treatment interruptions (TIs). Oxford’s Annette Oxenius collaborated with Swiss and Spanish investigators to trace HIV-specific immune responses in the Swiss-Spanish Intermittent Therapy Trial (SSITT).²²

The bottom line comes at the top of the article, in its title: “Stimulation of HIV-

specific cellular immunity by structured treatment interruption fails to enhance viral control of chronic infection.” Although HIV-specific CD4⁺ cells burgeoned during the study’s treatment breaks, only people with low pretreatment viral loads (below the group median of 30,976 copies/mL) maintained those gains. (Another study found that the retrovirus preferentially infects HIV-specific CD4⁺ cells during drug breaks.²³) The immune triggers recognized by cytotoxic T lymphocytes (CTLs) during and after TIs nearly mirrored those recognized before the TIs, a finding “indicating that [treatment interruptions] largely restored the pretherapy response and did not significantly alter the recognition profile within a patient.” As Oxenius notes, this limp CTL retort in people with chronic infection contrasts with broadening responses in people who try TIs after treatment of primary HIV infection.²⁴

After sifting these results and listing TI risks (acute retroviral syndrome, reseeded viral reservoirs, drops in CD4⁺ cells, HIV transmission, resistance, poor adherence to later therapy), the University of Pittsburgh’s Ume Abbas and John Mellors conclude that “risk should not be taken without reward.”²⁵

The Oxenius study takes a lot of steam out of the argument that puffed-up immune activation during TIs will abet viral control during chronic infection. Indeed, another study found that the best way to rebuild HIV-specific responses is to keep HIV under the tightest wraps possible. Comparing double PIs with single PI regimens in 49 people with acute or chronic infection, Australian researchers learned that “minimal immune activation, resulting from maximal suppression of viral replication, was required for long-term restoration and maintenance of Gag-specific T-cell responses.”²⁶ The 27 people who maintained better viral control with dual PIs had more than twice the chance of mounting HIV-specific CD4⁺ responses than did 22 people with poorer viral control while taking one PI ($P = 0.0222$).

If the immunologic rationale for TIs during chronic infection looks like a sand castle after high tide, drug breaks may still make sense as a way to ease or avert side effects, especially in people who began taking antiretrovirals at CD4⁺ counts and viral loads that no longer sound the start siren in recent guidelines. At least three studies now show that TIs are safest in people who began therapy

Table 4. Atorvastatin or fenofibrate for antiretroviral-induced hyperlipidemia

	Reference range	Baseline	Week 24	P
Atorvastatin (n = 20)				
Body mass index (kg/m ²)	—	25.4	25.0	NS
Total cholesterol (mg/dL)	200-239 (5.17-6.18 mmol/L) "borderline high"	299	218.5	0.0001
HDL-C (mg/dL)	35-60 (0.91-1.68 mmol/L)	42.3	43.9	NS
LDL-C (mg/dL)	60-130 (1.55-3.37 mmol/L)	203.8	127.5	0.0001
Triglycerides (mg/dL)	10-190 (0.11-2.15 mmol/L)	318.5	187.9	0.058
Fenofibrate (n = 20)				
Body mass index (kg/m ²)	—	24.1	24.3	NS
Total cholesterol (mg/dL)	200-239 (5.17-6.18 mmol/L) "borderline high"	256	219	0.008
Triglycerides (mg/dL)	10-190 (0.11-2.15 mmol/L)	812	377	0.0001

Source: Rosario Palacios, abstracts P140 and P141.

with decent T-cell tallies and enviable viral loads.²⁷⁻²⁹ Two Glasgow studies confirmed a bigger risk of bad TI results in people with higher loads or fewer T cells.

In a retrospective analysis of 56 people who took at least a two-month TI and then resumed treatment for at least 48 weeks, Nicola Gianotti (San Raffaele Scientific Institute, Milan) found that pre-TI viral load and CD4⁺ count and CD4⁺ cells at the time of the TI separated virologic responders from nonresponders [abstract PL6.3]. Most people, 87.5 percent, had a viral load above 400 copies/mL when they stopped therapy. Their pre-TI CD4⁺ counts and viral loads ranged from 162 to 543 cells/mm³ and from undetectable to 5.0 logs. Using a 48-week viral load below 400 copies/mL to define a good response, Gianotti counted 19 responders (34 percent) and 37 nonresponders (66 percent).

Nonresponders had a significant CD4⁺ drop during their TI, and 48 weeks after restarting treatment their CD4⁺ gain lagged that of responders by 100 cells/mm³ (111 versus 11 cells/mm³, *P* = 0.02). Gianotti could separate responders from nonresponders by their higher pre-TI CD4⁺ nadir (226 versus 128 cells/mm³, *P* = 0.0186), their higher CD4⁺ count when they stopped antiretrovirals (515 versus 285 cells/mm³, *P* = 0.0195), and their lower viral load before the TI (2.28 versus 2.93 logs, *P* = 0.05). In a multivariate analysis, a higher peak viral load before the TI (*P* = 0.006) and a shorter drug break (*P* = 0.05) favored a poor post-TI virologic response. Four people, all of

whom had suspended treatment with fewer than 200 cells/mm³, endured HIV-related "events" during their drug break.

In a Montreal cohort with much better virologic control when they stopped antiretrovirals, pretreatment nadir CD4⁺ emerged as the only independent predictor of a CD4⁺ drop below 200 cells/mm³ during the TI [abstract P25]. Nimâ Machouf (Clinique Médicale L'Actuel) prospectively tracked 83 people (75 of them gay men) who took at least a two-month TI after maintaining a sub-50-copy viral load with treatment. Their median CD4⁺ count when they quit was 660 cells/mm³ and their nadir CD4⁺ count 360 cells/mm³.

They lost an average 32 cells/mm³ monthly during the TIs, and the CD4⁺ count when they started the TIs correlated highly with how many T cells they lost (*r* = 0.394, *P* < 0.01). Fourteen people (17 percent) saw their CD4⁺ counts slide below 200 cells/mm³ during the TI, and only the nadir count predicted this outcome (*r*² = 0.57). Among 28 people who resumed therapy and had at least six months of follow-up, 26 regained a sub-50 viral load (after a median of 15 weeks). The two who didn't get back under 50 copies/mL had stopped treatment again after restarting.

Compared with the Italian study, this analysis confirms the relative safety of stopping treatment during tight virologic control in people who started therapy at higher CD4⁺ counts. Despite the four CD4⁺ dips below 200 cells/mm³, no one suffered a new AIDS diagnosis.

A study of mutant viral populations in 30 people taking a 14-week TI confirmed the (apparent) complete return of drug-sensitive virus in a minority of such groups [abstract P207]. Jacques Izopet (Hôpital Purpan, Toulouse) and coworkers at other sites studied 22 men and eight women with a median viral load of 4.21 logs (about 16,000 copies/mL) and CD4⁺ counts ranging from 212 to 733 cells/mm³ when they set sail on drug holidays.

In 10 people the mutant viral population did not change at all during the TI. Sixteen others had partial reversions to wild-type virus, maintaining mixed mutant populations. Only eight people (27 percent) had no mutant virus detectable in peripheral blood mononuclear cells (PBMCs) after 12 weeks without drugs. As other studies show, though, mutant species may persist at undetectable levels during prolonged drug holidays. Jonathan Schapiro (Stanford University and Tel Aviv University) suggested in Glasgow that resistance testing during a TI tests the assay's sensitivity better than it charts the waning of mutant virus. "You're not seeing disappearance of resistance mutations," he explained. "You're seeing the inability of the assay to detect [mutants] in small populations."

In the French study only people with some shift in mutant virus began a rescue regimen of efavirenz plus Trizivir (AZT, 3TC, and abacavir). In a switch-or-missing-data-equal failure analysis, nine of 17 people (53 percent) had a viral load below 400 copies/mL after 24 weeks of treatment. Among 10 people with a 24-week viral load under 50 copies/mL, seven had mutant virus in PBMCs during the TI. It's difficult, though, to rate the strategy's success in this group. Although everyone had key reverse transcriptase mutations (87 percent with T215Y and 50 percent with M184V), only 14 of the original 30 enrollees (47 percent) had a major nonnucleoside mutation. And Izopet did not report how many of the 24-week responders—if any—had mutations conferring resistance to efavirenz.

TWO NEW PIs, AND A T-20 TEE-OFF

Glasgow afforded fresh views of three drugs nosing their way nearer a spot on the pharmacy shelf: the fusion inhibitor T-20 and the PIs atazanavir and GW433908, the amprenavir prodrug.

T-20 tee-off: Don't wait till too late?

By next spring a Roche factory should be running full-bore, cranking out a freeze-dried powder called Fuzeon, or enfuvirtide, or, most familiarly, T-20. How fast this plant churns will be the rate-limiting factor determining how many take T-20, because plenty of people with multidrug-resistant virus may benefit from this hard-to-make, hard-to-take fusion inhibitor. So, despite T-20's likely high price, it will not lack early buyers. Two other questions about T-20's commercial rollout seem more important now:

1. Who are the best candidates for T-20?
2. How will they cope with the twice-daily shots?

Two savvy HIV clinicians who addressed the first question agree on the answer: Although many people with virus highly resistant to all current classes will surely want a crack at T-20, people starting "first salvage" stand to gain more. Chelsea and Westminster's Graeme Moyle uses the term "first salvage" to denote the last combination with a good chance to work for any given person. "Encouraging earlier initiation of enfuvirtide," he counsels, "may help diminish the risk of losing current options."³⁰ Moyle suggests colleagues may position a T-20 regimen as taking "something a bit more complex now to avoid something really tough next time."

New York clinician Howard Grossman echoes these sentiments more bluntly in an article by Mike Barr: "The best use will be when you're starting on what looks like your last good highly active regimen, not a crappy, cobbled-together salvage job."³¹ But because Roche expects to make only enough T-20 to treat 15,000 people in 2003, the drug may be rationed to those with the most resistant virus.

One reason T-20 looked good in two phase 3 trials^{32,33} involving hundreds of people with multiresistant virus is the drug many took with T-20: lopinavir. Multiple regression analysis of the North-and-South American study showed that people starting lopinavir with T-20 carved an extra quarter-log off their viral load ($P = 0.0348$).³⁴ But people who had tried lopinavir before the T-20 study added 0.83 log copies to their RNA tallies ($P < 0.0001$). The same analysis showed, not surprisingly, that people with less resistant virus and higher CD4⁺ counts got a bigger antiviral kick from T-20.

Table 5. Taking T-20 for 24 weeks: How easy? How hard?

	<i>Very easy</i>	<i>Easy</i>	<i>Neutral</i>	<i>Difficult</i>	<i>Very difficult</i>
Giving yourself injections (%)	30.7	37.4	18.6	9.8	3.5
Dissolving medication in water (%)	39.4	35.0	14.0	9.7	1.9
	<i>None of the time</i>	<i>A little of the time</i>	<i>Some of the time</i>	<i>Most of the time</i>	<i>All of the time</i>
How often did injections interfere with daily activities? (%)	30.1	28.9	27.7	9.8	3.5
How often did injection effects interfere with daily activities? (%)	53.7	20.8	18.8	5.5	1.2
	<i>Not at all</i>	<i>A little</i>	<i>Moderately</i>	<i>Quite a bit</i>	<i>Extremely</i>
Have injections reduced satisfaction with physical appearance? (%)	44.7	30.7	13.5	8.1	3.2

Source: Jesse Green, abstract P48.

The certain advantage of starting T-20 with other novel agents raises a third question, Bernard Hirschel observed in Glasgow: No one knows how well it will meld with drugs like the PI tipranavir, the nonnucleoside TMC 125, or integrase inhibitors. Hirschel added another unknown—how long it will work. The phase 3 trials lasted 24 weeks.

Besides its Beverly Hills price tag, the biggest bugbear with T-20 will be taking it. Except for people who have sampled recombinant growth hormone or done penance with IL-2, few folks with HIV have had to give themselves regular injections. Can they cope? A comprehensive survey of 600 phase 3 trial enrollees suggests that most can [abstract P48]. Roche's Jesse Green reported that substantial majorities claimed T-20 wasn't that hard to take and didn't interfere much with quotidian pursuits like going to work and having sex (Table 5). And the good response rate didn't slip between study weeks 4 and 24.

Still, after 24 weeks of twice-daily shots, sizeable minorities had gripes: 31.5 percent complained that taking T-20 complicated traveling "moderately, quite a bit, or extremely," and another 18.7 percent said it complicated traveling "a little." While 29.9 percent felt T-20 interfered with maintaining privacy "moderately, quite a bit, or extremely," another 25 percent said it did so "a little." More than 20 percent thought taking T-20 impeded recreation or sex "moderately, quite a bit, or extremely."

Since clinical trial volunteers tend to be a tough-it-out breed, T-20 complaints from rank-and-file HIV contingents will likely gain frequency and volume. The

survey population consisted largely of whites (89.3 percent) and gay men (65.4 percent), who typically enjoy greater support and access to information than others with HIV.

Wisely anticipating difficulties in taking T-20, Roche has launched a how-to campaign. The curtain-closer at Roche's Glasgow symposium was Nicky Perry, an HIV nurse from Brighton already well versed in T-20 tips and technicalities. Among the points she made:

- Reconstitution of T-20 in sterile water can take up to 45 minutes for beginners.
- Although morning and evening doses can be reconstituted at the same time, the evening batch must be refrigerated and brought to room temperature before use.
- Different injection sites should be used for each injection, a challenge for lean people.
- Injections should be slow and *not* into muscle.
- Gently massaging the injection site up to five minutes after the shot helps disperse the drug.
- Applying a cold pack after the shot can quell inflammation.
- When flying, a person must carry the T-20 kit on board. Cargo holds are too cold.

So using T-20 won't be a snap. But will it be a snarl? Graeme Moyle doesn't think so, noting that young people with type 1 diabetes—faced with lifelong insulin shots—generally trade the burden for the benefits.³⁰ His own experience with growth hormone, IL-2, and T-20 indicates that "injectables are readily accepted, even in healthy persons, when

the patient is well educated about the therapy—its favorable as well as its adverse effects—and the therapy has effects that are easily observed.” For growth hormone and IL-2, those effects are gains in weight and CD4⁺ cells; for T-20, it should be a lower viral load.

Northwestern University’s Robert Murphy voiced the unhappy irony that, at a time when drug developers aim for simpler antiretrovirals, T-20 breaks the mold. But a greater irony—and this time a happy one—emerged in a Glasgow talk by Elly Katabira from Makerere University in Kampala [abstract PL4.1]. Without mentioning T-20, he noted that many Ugandans would probably be happier with a daily antiretroviral shot than with a hodgepodge of pills. Moyle makes the same point about his London cache-ment: “For some patients, a simple and well-tolerated injection may be more agreeable than yet more pills.”³⁰

Even if those twice-daily needles prove too prickly for some, they may not prove intolerable. As Mike Barr astutely observes, “HIVers are famous for putting up with a lot to stay healthy.”³¹

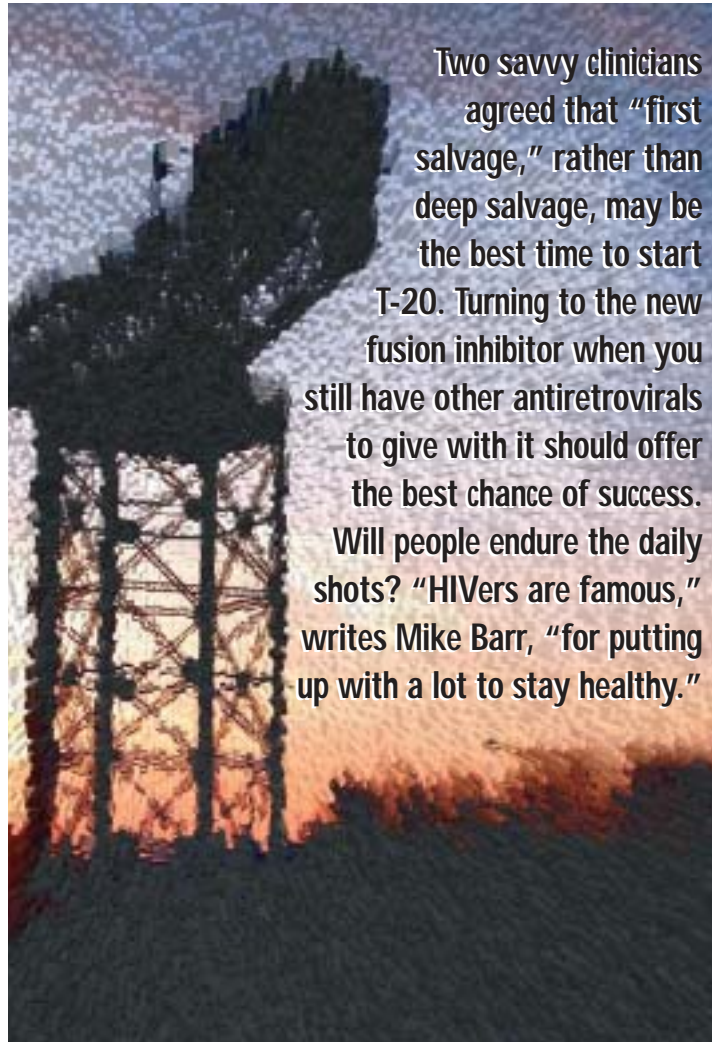
Atazanavir meets the Mercedes

Atazanavir, the once-daily PI from Bristol-Myers Squibb, raised eyebrows and dropped jaws when it brought viral loads below 50 copies/mL in only 32 percent of treatment-naïve people in a 48-week intent-to-treat analysis.³⁵ This startling placebo-controlled comparison with efavirenz (plus Combivir in both arms) also found that the nonnucleoside notched a feeble 48-week sub-50 score, 37 percent. The 48-week sub-400-copy measures came closer to the realm of reason, 70 percent for atazanavir and 64 percent for efavirenz.

“This is really very strange,” suggested the University of Geneva’s Bernard Hirschel while reviewing the results in Glasgow [presentation KL3]. Everyone knows something screwy happened in this study—because efavirenz has done so much better in a half-dozen previous

trials—but no one knows exactly what. Efavirenz has so loaded its randomized trial trophy shelf that clinicians aren’t likely to abandon the drug just because of this study. But the atazanavir results should, at the very least, foment some stimulating forensics at the drug’s approval hearing.

In his Glasgow keynote talk, Hirschel became the first clinician of note to suggest in public that there’s something funny about this emperor’s new clothes. Though atazanavir’s antiviral fabric may be tangible, the fit will look loose until researchers can explain these results.



Two savvy clinicians agreed that “first salvage,” rather than deep salvage, may be the best time to start T-20. Turning to the new fusion inhibitor when you still have other antiretrovirals to give with it should offer the best chance of success. Will people endure the daily shots? “HIVers are famous,” writes Mike Barr, “for putting up with a lot to stay healthy.”

And that didn’t happen in a detailed Glasgow poster hung by Jean-François Delfraissy (Hôpital di Bicêtre, Paris) [abstract P36]. As in earlier reviews of this study, the unsatisfactory conclusion stressed the “similar efficacy” of once-daily atazanavir and once-daily efavirenz.

Hirschel acknowledged one factor that could contribute to the poor virologic responses—different versions of the Roche assay used to tote circulating virus.

Researchers in North and South America relied on version 1.0, while Europe, Africa, and Asia used version 1.5, which spots non-B subtype viruses better than version 1.0. A 24-week analysis that Bristol-Myers gave Hirschel shows about a 55 percent sub-50 rate with version 1.0 versus about 45 percent with version 1.5.

But that difference can’t completely explain the low 48-week scores, Hirschel said, resorting to an automotive analogy. When atazanavir matched nelfinavir in an earlier randomized study, proponents could claim that “our car is as good as a VW.” Now, after taking on high-octane efavirenz, they can say “our car is as good as a Mercedes . . . but both went only 32 miles per hour.” To understand why, Hirschel offered, one must do more than blame the speedometer.

Poor adherence by some people at the 91 sites (on every continent except Australia and Antarctica) seems a more credible explanation at this point. Delfraissy reported the following mutation rates in people who suffered a virologic failure:

- Among 20 genotyped people taking efavirenz, 13 (65 percent) had the K103N mutation.
- Among 25 genotyped people taking atazanavir, 14 (56 percent) had the M184V mutation conferring resistance to 3TC.
- Among 20 genotyped people taking efavirenz, 12 (60 percent) had M184V.

Atazanavir’s signature mutation, I50L, turned up in only three of 25 genotyped people (12 percent) taking the PI. But even that rate may seem high given the slow accrual of protease mutations as a regimen fails, compared with mutations to 3TC or a nonnucleoside. More detailed analyses of resistance in this study’s 800 participants should prove informative. And most everyone hopes that information will prove exculpatory because the efavirenz trial also confirmed atazanavir’s sleek lipid profile.

Table 6. Arguments for and against global antiretroviral access

<i>Against</i>	<i>For</i>
Prevention should be the priority.	Wider antiretroviral access should facilitate, rather than impede, prevention.
Antiretrovirals are not affordable.	Antiretrovirals can now be made available at affordable prices in developing countries.
Antiretrovirals are not cost-effective.	Studies in Brazil prove the cost-effectiveness of antiretrovirals.
Effectiveness, tolerability, and adherence in the developing world are questionable.	Studies demonstrate equivalent effectiveness, tolerability, and adherence in South and North.
Poor countries don't have the healthcare infrastructure to deliver antiretrovirals.	Access to antiretrovirals will create support for strengthening healthcare infrastructure.
The risk of transmitting resistant virus is too high.	Early studies show no higher incidence of resistance in developing countries.

Source: Michel Kazatchkine, presentation KL1.

GW still racing the VW

If atazanavir deserves credit for matching its merits against the Mercedes of antiretrovirals, efavirenz (see preceding section), Glaxo's new PI candidate picked on the VW, nelfinavir, for its first two dashes to a 48-week checkered flag. Partly because of that choice, the results looked checkered to some critics of this randomized, open-label study in treatment-naïve people. And the results matter because, when boosted by ritonavir, GW433908 ("908" for short) will join amprenavir as atazanavir's once-daily competition in the PI sweepstakes, and 908 may also have *laissez-faire* leanings toward lipids. The prodrug of amprenavir, 908 needs a dose of only two 700-mg tablets daily when given with two 100-mg ritonavir caps. No food or fluid restrictions apply.

The trial enrolled nearly 650 treatment-naïve people from Germany, South Africa, and the United States [abstract PL14.4]. Dirk Schürmann (Charité University Hospital, Berlin) reported median baseline numbers of 166 cells/mm³ in the 908 arm and 177 cells/mm³ in the nelfinavir arm, and respective viral loads of 4.78 and 4.83 logs (about 63,000 copies/mL). Everyone also took abacavir and 3TC. In a missing-data-equal-failure analysis, 68 percent taking 908 and 65 percent taking nelfinavir had a 48-week viral load under 400 copies/mL. The sub-50-copy rates with the same analysis were 56 percent for 908 and 52 percent for nelfinavir. The median CD4⁺ count rose about 200 cells/mm³ in both arms.

While 15 percent taking nelfinavir

never got their viral load under 400 copies/mL or did and rebounded, only 4 percent taking 908 had a virologic failure defined this way. But 25 percent quit the 908 arm compared with 15 percent in the nelfinavir arm. The raw numbers don't explain this gap. Toxicity made 8 percent abandon 908 and 5 percent stop nelfinavir. And 908 edged nelfinavir in all those gray-zone grounds for quitting: lost to follow-up, consent withdrawn, protocol violation, and "other." Joep Lange (Academic Medical Center, Amsterdam) contested Schürmann's assertion that dropouts in the 908 arm could not be tied to the drug.

Lange and others also puzzled over the resistance mutation analysis among 32 people taking 908 and 54 taking nelfinavir who had ongoing viral replication during the study. Whereas no primary or secondary protease mutations arose in the 908 group, 30 of 54 taking nelfinavir (56 percent) saw such mutations emerge ($P < 0.001$). One may assume, then, that reverse transcriptase (RT) mutations must explain some of the 908 failures. But RT changes appeared in only three of 32 (9 percent) in the 908 arm compared with 31 of 54 (57 percent) in the nelfinavir arm ($P < 0.001$). Lange labeled these findings in the 908 group "impossible" unless researchers ran the resistance tests at the wrong time.

While 6 percent taking 908 had grade 3 or 4 triglyceride elevations, 2 percent taking nelfinavir had high triglycerides. Only one person in either arm had seriously elevated cholesterol or glucose. Proportions with levels of protective HDL

cholesterol rose substantially in both groups.

Another randomized, open-label trial presented earlier in the year also compared 908 (1,400 mg twice daily without ritonavir) with standard-dose nelfinavir plus abacavir and 3TC in treatment-naïve people.³⁶ After 24 weeks a missing-data-equal-failure analysis counted 73 percent taking 908 and 54 percent taking nelfinavir with viral loads under 400 copies/mL. Respective sub-50-copy rates were 54 percent and 40 percent. In this study, unlike the one presented in Glasgow, dropouts proved more common with nelfinavir (28 percent by week 24) than with 908 (19 percent). Lipid elevations were rare in either arm through 24 weeks. As David Cooper noted in Glasgow, however, clinicians will want to see how 908 stacks up against one of today's top drugs, efavirenz or lopinavir.

MAKING WAY FOR THE "A" WORDS

It's hard—maybe impossible—to survive any international HIV meeting these days without hearing a few good talks on global access to antiretrovirals. But the other "A" word, adherence, turns up in poster halls more than plenary sessions, maybe because HIV docs bought the adherence message years ago. But if they bought it, how well are they selling it? Perhaps not too well, the Glasgow organizers apparently surmised, because they gave adherence and access equal billing.

Two of Glasgow's keynote talks touched on antiretroviral access—one directly, and one indirectly. Michel Kazatchkine (Agence Nationale de Recherches sur le SIDA [ANRS], Paris) met arguments against fast access head-on (Table 6), charging that double standards in the West offer cozy—but specious—rationales against widespread antiretroviral therapy [presentation KL1]. Fears of rampant resistance once antiretrovirals see wider use in Africa and Asia strike Kazatchkine as particularly duplicitous, since ever-evolving resistance in Europe and North America have sparked no clamor for withholding therapy there. The risk of transmitting resistant virus will be worse in poorer countries, he maintained, with haphazard, piecemeal access than with well-planned and well-monitored programs.

But wouldn't a sharper focus on vaccine development than on access stem the epidemic more quickly? Yes, if such a vaccine were anywhere close to ready. And a cold dose of reality from Jaap Goudsmit (Academic Medical Center, Amsterdam) made it clear that everyone's still waiting [presentation KL2]. He made three somber points:

- Induction of neutralizing antibodies is necessary and sufficient to prevent HIV infection.
- We do not know how to induce neutralizing antibodies.
- Induction of T-cell immunity is necessary and sufficient to prevent AIDS, but not to prevent HIV infection.

Few expect any good news from efficacy trials of VaxGen's antibody-stimulating vaccine. So today's only viable candidates, Goudsmit maintained, are vaccines that stir T-cell immunity. Progress with these vaccines remains steady but slow. And modeling by Goudsmit's group shows that the later you start giving a T-cell vaccine in the epidemic's course, the fewer long-term nonprogressors you create. He did not have to spell out the salient corollary of this finding: Antiretrovirals can create lots of long-term nonprogressors right away.

Glasgow's pharmacology session featured one talk that bolstered Kazatchkine's argument on antiretroviral affordability. Cipla, the Indian generic manufacturer, dispatched J.A. Gogtay to report that a three-in-one pill embracing d4T, 3TC, and nevirapine matches the pharmacokinetics of branded versions of those drugs given individually [abstract PL8.4]. A randomized, single-dose crossover study in 28 healthy volunteers showed equivalent bioavailability between the Cipla product, called Trioimmune, and standard doses of d4T, 3TC, and nevirapine. Cipla has also devised a version of the product containing 30 mg of d4T instead of 40 mg for people weighing less than 60 kg. But there is no version with 100 mg instead of 200 mg of nevirapine, so people trying Trioimmune will have to take the three drugs separately for the first two weeks. Treatment with Trioimmune will cost less than \$1 a day.

Reviewing early results of Botswana's national antiretroviral program, the Ministry of Health's Ernest Darkoh-Ampen buttressed Kazatchkine's contention that

the equator does not divide good from bad adherers [abstract PL4.3]. The pilot program has enrolled 2,867 people at four sites and started treating 2,142 of them. So far, appointment-keeping adherence measures 97 percent. The cohort's pre-treatment CD4⁺ count averaged 50 cells/mm³, and because the waiting time between enrollment and the first dose ran from six to eight weeks, 7 percent of enrollees died as staffers struggled to meet their needs. But Darkoh anticipates that the next wave of enrollees will include fewer seriously ill people who will require less intense follow-up.

A government-sponsored study figured that 110,000 people in Botswana qualify for treatment because they have an AIDS illness or fewer than 200 CD4⁺ cells/mm³. But the country could not hope to treat them all. Generous outside funding helped buy antiretrovirals and build four clinics; the bottleneck has been training staff. But as more streamlined training takes hold, Darkoh believes Botswana stands poised to open four more HIV centers in the next year.

There is nothing unique about the resolute commitment of people in Botswana to their treatment program. The ANRS-sponsored effort in Senegal charted an 87.9 percent adherence rate among 58 people starting antiretrovirals.³⁷ In a Cape Town cohort of 289 people, 42 percent of whom live in "informal dwellings or shacks," Catherine Orrell measured an 87.2 percent adherence rate.³⁸ The strongest predictor of poor adherence was not poverty or its byproducts, but taking a three-times-daily regimen.

Except for the "informal dwellings or shacks," how very "Northern" Cape Town sounds. Or, perhaps, adherence will be *better* in the South than in the North if, as Michael Kazatchkine argued, antiretrovirals reach people through well-planned programs rather than through black markets. Kathleen Squires (University of Southern California, Los Angeles), who presented the atazanavir-efavirenz trial in the United States earlier in 2002,³⁵ told *IAPAC Monthly* that preliminary evidence suggests better adherence in Africa and Asia than in Western Europe.

In five Western European countries, a survey of 504 people found that those taking once-daily therapy had a much better record of remembering to take their antiretrovirals [abstract P99]. Graeme Moyle (Chelsea and Westminster Hospital,

London) found that 66 percent taking a thrice-daily regimen and 63 percent taking a twice-daily regimen admitted forgetting to take their antiretrovirals. Among those taking once-daily therapy, only 40 percent said they missed doses.

Although 81 percent of respondents from France, Germany, Italy, Spain, and the United Kingdom claimed to be "extremely" (62 percent) or "somewhat" (19 percent) interested in once-daily dosing, they were precise about how many pills they would down in one sitting. While 92 percent said they preferred to take a three-pill regimen "all at once" and 84 percent said the same about four pills, only 59 percent wanted to take six pills all at once, 38 percent eight pills, and 31 percent more than eight pills.

And the roster of once-daily antiretrovirals continues to grow, Moyle noted in a satellite symposium. Besides efavirenz, ritonavir-boosted amprenavir, ddI, 3TC, and tenofovir, clinicians may also soon be able to choose from extended-release d4T (d4T-XR), nevirapine, other boosted PIs, atazanavir, and the nucleoside FTC (perhaps combined in one pill with tenofovir). As recently as the turn of the century, he added, the next regimen in a sequence almost always meant a more complex regimen—with more pills, more frequent dosing, and/or food restrictions. Today, sequential regimens can preserve first-line simplicity, for example:

- ddI/3TC/efavirenz Once daily, fasted, three or four pills
- d4T-XR/tenofovir/atazanavir Once daily, food, four pills
- abacavir/tenofovir/lopinavir Twice daily

But pharmacologic facility means little for the perpetually forgetful. Simpler regimens are crucial to better adherence, Jonathan Schapiro agreed in a plenary talk on the topic [presentation PL5.1]. But they don't solve the problem. Part of that problem, he reminded colleagues, is the near-total lack of adherence training for HIV clinicians. He proffered a simple three-step program:

1. The treated person must help pick the treatment.
2. Adherence must be formally monitored.
3. Support must be continuous.

Formal monitoring, Schapiro elaborated, need not mean MEMS Caps, pill counts, or Inquisitional questionnaires. Studies show that adherence gauged by simple self-reports correlates highly with results garnered from more exacting exercises.^{39,40}

A 294-person study presented in Glasgow by Maria Paola Trotta (National Institute of Infectious Diseases, Rome) found significant correlations between self-reports of adherence (on a 16-item questionnaire), drug concentrations ($P = 0.02$), and sub-500-copy virologic responses ($P = 0.03$).

How much adherence is enough? As with CD4⁺ counts, viral loads, and resistance, Schapiro proposed, there are no absolute cutoffs. Saying that a person must take all doses on time at least 90 to 95 percent of the time is too simplistic, he argued, because regimens differ in how quickly missed doses promote replication of resistant virus.

How often should resistance be monitored? Again, no one has set in stone the optimal interval for measuring CD4⁺ cells, HIV RNA, or viral susceptibility to drugs. And no one knows how often clinicians must replay the adherence rule book. Adherence may not have to be checked at every visit, Schapiro offered. But, as with CD4⁺ counts and viral loads, it has to be checked regularly.

Julio Montaner and colleagues have reaped sheaves of rich data from their closely monitored British Columbian cohort. They have studied the effects of CD4⁺ count, viral load, and double or triple regimens with or without PIs or NNRTIs on HIV disease progression and death. One factor, he stressed in Glasgow, means more than any single drug in separating the sick from symptom free, the quick from the dead, in two or three years. Adherence. ■

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

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A B S T R A C T S

Clinical Infectious Disease

Prevention of human immunodeficiency virus-related opportunistic infections in France: A cost-effectiveness analysis.

Y Yazdanpanah et al.

A simulation model of human immunodeficiency virus (HIV) disease, which incorporated French data on the progression of HIV disease in the absence of antiretroviral therapy and on cost, was used to determine the clinical impact and cost-effectiveness of different strategies for the prevention of opportunistic infections in French patients who receive highly active antiretroviral therapy (HAART). Compared with use of no prophylaxis, use of trimethoprim-sulfamethoxazole (TMP-SMX) increased per-person lifetime costs from euro 185,600 to euro 187,900 and quality-adjusted life expectancy from 112.2 to 113.7 months, for an incremental cost-effectiveness ratio of euro 18,700 per quality-adjusted life-year (euro/QALY) gained. Compared with use of TMP-SMX alone, use of TMP-SMX plus azithromycin cost euro 23,900/QALY gained; adding fluconazole cost an additional euro 54,500/QALY gained. All strategies that included oral ganciclovir had cost-effectiveness ratios that exceeded euro 100,000/QALY gained. In the era of HAART, on the basis of French data, prophylaxis against *Pneumocystis carinii* pneumonia, toxoplasmic encephalitis, and *Mycobacterium avium* complex bacteremia is cost-effective. Prophylaxis against fungal and cytomegalovirus infections is less cost-effective than are other therapeutic options for HIV disease and should remain of lower priority.

Clin Infect Dis 2003;36(1):86-96.

Journal of Acquired Immune Deficiency Syndromes

Results of a Phase 2 clinical trial at 48 weeks (AI424-007): A dose-ranging, safety, and efficacy comparative trial of atazanavir at three doses in combination with didanosine and stavudine in antiretroviral-naïve subjects.

I Sanne et al. (AI424-007 Clinical Trial Group)

Three dose levels of the protease inhibitor (PI) atazanavir (200, 400, and 500 mg once daily) were compared with nelfinavir (750 mg three times daily) when given both as monotherapy and in combination with didanosine and stavudine in 420 antiretroviral-naïve subjects infected with HIV-1. Subjects received monotherapy for two weeks, followed by combination therapy for 46 weeks. After 48 weeks, mean change from baseline in HIV RNA (-2.57 to -2.33 log copies/mL), the proportion of subjects with HIV RNA <400 copies/mL (56 percent to 64 percent) and

<50 copies/mL (28 percent to 42 percent), and mean increases in CD4 cell count (185-221 cells/mm³) were comparable across treatment groups. Diarrhea was two to three times more common in the nelfinavir group (61 percent of subjects) than in the atazanavir groups (23 percent to 30 percent of subjects, <.0001 versus nelfinavir), and jaundice occurred only in atazanavir-treated subjects (6 percent, 6 percent, and 12 percent in the 200-, 400-, and 500-mg groups, respectively) (<.03 for all atazanavir regimens versus nelfinavir). Mean percent change from baseline in fasting low-density lipoprotein (LDL) cholesterol was significantly less in the atazanavir groups (-7 percent to 4 percent) than in the nelfinavir group (31 percent) (<.0001). In conclusion, once-daily atazanavir is a potent, safe, and well tolerated PI that rapidly and durably suppresses HIV RNA and durably increases CD4 cell count in antiretroviral-naïve subjects. Through 48 weeks, atazanavir was not associated with clinically relevant increases in total cholesterol, fasting LDL cholesterol, or fasting triglycerides. In comparison, nelfinavir was associated with prompt, marked, and sustained elevations in these parameters of a magnitude that suggests they are clinically relevant.

J Acquir Immune Defic Syndr 2003;32(1):18-29.

Antimicrobial Agents and Chemotherapy

Pharmacokinetic-pharmacodynamic analysis of lopinavir-ritonavir in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in extensively pretreated human immunodeficiency virus-infected patients.

A Hsu et al. (Global Pharmaceutical Research and Development, Abbott Laboratories)

The steady-state pharmacokinetics and pharmacodynamics of two oral doses of lopinavir-ritonavir (lopinavir/r; 400/100 and 533/133 mg) twice daily (BID) when dosed in combination with efavirenz, plus two nucleoside reverse transcriptase inhibitors, were assessed in a phase II, open-label, randomized, parallel arm study in 57 multiple protease inhibitor-experienced but non-nucleoside reverse transcriptase inhibitor-naïve human immunodeficiency virus (HIV)-infected subjects. All subjects began dosing of lopinavir/r at 400/100 mg BID; subjects in one arm increased the lopinavir/r dose to 533/133 mg BID on day 14. When codosed with efavirenz, the lopinavir/r 400/100 mg BID regimen resulted in lower lopinavir concentrations in plasma, particularly C_{min} , than were observed in previous studies of lopinavir/r administered without efavirenz. Increasing the lopinavir/r dose to 533/133 mg increased the lopinavir area under the concentration-time curve over a 12-h dosing interval (AUC(12)), $C_{predose}$, and C_{min} by 46, 70, and 141%, respectively. The increase in lopinavir C_{max} (33 percent) did not

reach statistical significance. Ritonavir AUC(12), C_{max} , $C_{predose}$, and C_{min} values were increased 46 percent to 63 percent. The lopinavir predose concentrations achieved with the 533/133-mg BID dose were similar to those observed with lopinavir/r 400/100 mg BID in the absence of efavirenz. Results from univariate logistic regression analyses identified lopinavir and efavirenz inhibitory quotient (IQ) parameters, as well as the baseline lopinavir phenotypic susceptibility, as predictors of antiviral response (HIV RNA <400 copies/ml at week 24); however, no lopinavir or efavirenz concentration parameter was identified as a predictor. Multiple stepwise logistic regressions confirmed the significance of the IQ parameters, as well as other baseline characteristics, in predicting virologic response at 24 weeks in this patient population.

Antimicrob Agents Chemother 2003;47(1):350-9.

BMC Public Health

Endemic cryptosporidiosis and exposure to municipal tap water in persons with acquired immunodeficiency syndrome (AIDS): A case-control study.

TJ Aragon et al.

In persons with acquired immunodeficiency syndrome (AIDS), *Cryptosporidium parvum* causes a prolonged, severe diarrheal illness to which there is no effective treatment, and the risk of developing cryptosporidiosis from drinking tap water in non-outbreak settings remains uncertain. To test the hypothesis that drinking tap water was associated with developing cryptosporidiosis, we conducted a matched case-control study among persons with AIDS in San Francisco. Among patients reported to the San Francisco AIDS Registry from May 1996 through September 1998, we compared patients who developed cryptosporidiosis to those who did not. Cases were individually matched to controls based on age, sex, race/ethnicity, CD4 T lymphocyte count, date of CD4 count, and date of case diagnosis. Population attributable fractions (PAFs) were calculated. The study consisted of 49 cases and 99 matched controls. In the multivariable analysis with adjustments for confounders, tap water consumption inside and outside the home at the highest exposure categories was associated with the occurrence of cryptosporidiosis (inside the home: odds ratio (OR), 6.76; 95 percent CI 1.37 to 33.5, and outside the home: OR 3.16; 95 percent CI 1.23 to 8.13). The PAF was 85 percent; that is, the proportion of cases of cryptosporidiosis in San Francisco AIDS patients attributable to tap water consumption could have been as high as 85 percent. Although the results from this observational study cannot be considered definitive, until there is more data, we recommend persons with AIDS, especially those with compromised immune systems, consider avoiding tap water.

BMC Public Health 2003;3(1):2.



I N T H E L I F E



Claire Touchie

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 Claire Touchie, Assistant Professor, Division of General Internal Medicine and Infectious Diseases at the University of Ottawa, The Ottawa Hospital, Canada.

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

"Tout arrive à point à qui sait attendre."
[Everything comes to those who wait.]

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

Family life with time for my husband and daughter. I am particularly fond of gardening and cooking.

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

The south of France for the heat, coloring, lavender scent, and food—Canada for everything else.

Who are your mentors or real life heroes?

Dr. Tom Marrie for guiding me in my career and Dr. Dale Dauphinée for listening.

With what historical figure do you most identify?

Not answered.

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

Marguerite Yourcenar for her rendition of medieval medicine; Stewart McLean, a Canadian author, for making me laugh; and J.S. Bach for his unmatched talent.

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

Medieval Europe, because women played an active role and had influence on day-to-day life.

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

An anthropologist or a chef.

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

Antibiotics and vaccines, amongst many. A repeat failure, which is almost predictable, is war.

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

I believe that we are entering a dark age of humanity with more battles between the richer and poorer nations with an eventual fall of life, as we know it. ■



[Strength in Numbers]

[IAPAC Welcomes New and Renewing Members]

In November and December 2002, the International Association of Physicians in AIDS Care (IAPAC) welcomed 70 new and renewing dues-paying members from eight countries. IAPAC thanks the following physicians and allied health workers for their support of the association's mission to improve the quality of care provided to men, women, and children who are living with HIV/AIDS.

Bruce D. Agins, *USA*
Akbar Y. Badat, *Zambia*
Nicholaos Bellos, *USA*
Paul Benson, *USA*
Leonard Berkowitz, *USA*
Eric Capulla, *USA*
Joseph Cervia, *USA*
Alfonso Chan, *USA*
Paul J. Cimoch, *USA*
Calvin Cohen, *USA*
Douglas Cunningham, *USA*
Elizabeth Dax, *Australia*
Judith A. Delmar, *USA*
Gary DeSimone, *USA*
David D'Hansel, *USA*
Wayne Dodge, *USA*
J. Yusaf Erskine, *USA*
Victor Fainstein, *USA*
Getachew Feleke, *USA*
Donna Gallagher, *USA*
Joseph C. Gathe, Jr., *USA*

James Groundwater, *USA*
Debra Gutterman, *USA*
David Herman, *USA*
Claire Hicks, *USA*
Joseph Jemsek, *USA*
Joseph F. John, Jr., *USA*
Steven Johnson, *USA*
Michael Kaiser, *USA*
Mary J. Kasten, *USA*
Jeffrey Kirchner, *USA*
Patricia Kloser, *USA*
Eduardo Leyva, *Colombia*
Arthur Stanley Link Jr., *USA*
Joseph Marzouk, *USA*
Arthur Moswin, *USA*
Roberto I. Narimatsu, *USA*
Mark Netherda, *USA*
Paul Samuel Pegram, *USA*
Gerald Pierone, *USA*
Scott Remick, *USA*
Judith A. Riley, *USA*
Carlos Ruiz, *USA*
Richard Rutstein, *USA*
James H. Sampson, *USA*
Adrian Rivero Santos, *Mexico*
Ronald Schut, *USA*
Robert Schwartz, *USA*
Joel Sender, *USA*
Peter Shalit, *USA*
Eyesusawit Shewangizaw, *Ethiopia*
Nancy Shulman, *USA*
Morton Singer Jr., *USA*

Mark Smith, *USA*
Charles Steinberg, *USA*
Denise Sutherland, *USA*
Sharon Tear, *USA*
Claire Touchie, *USA*
Thanes Vanig, *USA*
Peter E. Vink, *USA*
David Wheeler, *USA*
Ryan Zane, *USA*
Nelson Zide, *USA*

Also, the following institutions renewed their institutional memberships: the CDC-NPIN Resource Center; New York Public Library; Canadian AIDS Treatment Information Exchange (CATIE); Tav Bibliotheek; and Wayne State University Medical Library. Both Boehringer Ingelheim and Gilead Sciences renewed their Corporate Partner status, which allows them to support ongoing activities and to subsidize IAPAC professional memberships for developing world physicians.

To learn more about professional and institutional memberships, call (312) 795-4934 or send an e-mail to member@iapac.org. For information regarding Corporate Partner opportunities, call (312) 795-4941 or send an e-mail to partner@iapac.org.

[Recruit your colleagues to join IAPAC]

Health professionals who join the International Association of Physicians in AIDS Care (IAPAC) benefit from the research and expertise disseminated through the association's journals, Web site, care tools, and annual symposia. Greater membership in IAPAC also means more support for the association's training programs. These programs are making great strides in helping professionals learn best practice care techniques in the developing world, where the pandemic is taking its heaviest toll. Finally, as IAPAC continues to find strength in numbers, and represent more and more of the

world's health professionals, expanded membership means a more powerful voice in discussions that can lead to increased funding for medications, more effective inter-organizational cooperation, and simply better quality of life for those living with HIV disease.

These reasons should be more than enough to encourage you to recruit colleagues to join IAPAC. Nonetheless, we want to provide you with personal rewards for your recruitment efforts.

Through the end of 2003, every new recruit who lists you as the member who referred him/her to IAPAC brings you

closer to winning free travel and/or a complimentary membership extension. For each member you recruit, your name will be entered in a drawing for one roundtrip airline ticket within your continent or region of the world. If you recruit five new members before the end of the year, you will receive 12 months of dues-free membership.

Battling complacency and advancing commitment in the international struggle against HIV/AIDS requires a strong, coordinated effort. Encourage your colleagues to join that effort as members of IAPAC.



SAY ANYTHING



Warnings that patients would skip doses and create drug-resistant strains of the disease—expressed last year by top US foreign aid official Andrew S. Natsios—have not been borne out. The program’s adherence rates seem significantly higher than those at treatment centers in the West...

Washington Post reporter Michael Grunwald in a December 2, 2002, article profiling Botswana’s ambitious AIDS treatment and prevention program, which he termed “the developing world’s most intense attack on AIDS.” The program promises antiretroviral therapy to all who need it. While Botswana’s efforts have been rewarded with very good adherence rates, according to the article, there have been problems with hospital overcrowding, and officials said they have failed to convince a majority of citizens to change sexual behaviors or get tested for HIV. Botswana currently has one of the highest HIV prevalence rates in the world.



According to [official Chinese news agency] Xinhua, four drugs—zidovudine, didanosine, stavudine, and nevirapine—would be available in China soon, and mass production would reduce annual treatment expense for each AIDS patient by 90 percent. The annual expense for each patient is set to be around 3,000 and 5,000 yuan (US\$360-600).

Reuters Health reporting December 30, 2002, that the Chinese government announced plans to mass-produce four generic antiretroviral agents beginning in January 2003. China only officially acknowledged its burgeoning HIV crisis in the last months of 2002. The director of a Beijing AIDS treatment facility told Reuters Health that he had not yet received notification of when the more affordable drugs would be available to patients.



It’s perfectly legal to teach sex education in Louisiana schools, but only one of our 66 parishes actually does. We don’t like to talk about it.

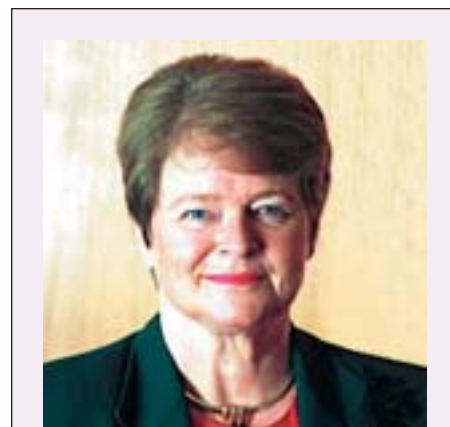
Louisiana State Senator Paulette Riley Irons describing a cultural disinclination in her state for frank discussions of sex, as quoted in a December 11, 2002, Kaiser Family Foundation special report. This is seen as one of several factors leading to a 9 percent increase in new HIV infections in the Southern region of the United States (comprised of 16 states plus the District of Columbia) in 2000-2001. The rest of the country averaged a 1 percent increase in new HIV infections during that same period. Other factors seen as contributing to the region’s disproportionately high HIV incidence include unequal access to healthcare for minority populations; geographical barriers where housing and healthcare spread sparsely over vast regions makes it difficult to reach clinics and hospitals; a high prevalence of sexually transmitted diseases; and immigration of HIV-infected people from other regions.



Looking after orphans is like starting life all over again, because I have to work on the farm, clean the house, feed the children, buy school uniforms. I thought I would no longer do these things again. I am not sure if I have the energy to cope.

A 65-year-old man in Makoni Manicaland, Zimbabwe, who was left to care for three children after their parents died of AIDS-related complications. He was quoted in a World Health Organization (WHO) report that examined the impact of AIDS on elderly men and women who must care for younger HIV-infected people and the orphans of family members who have died of HIV disease. The report was based on a case study of 685 older Zimbabweans who are performing this type of care. It

found that such caregivers are often financially burdened because they lack support they might otherwise receive from their adult children who are dying or dead; their poverty is compounded by having to pay for the everyday and medical needs of their children and grandchildren.



I managed to bring health onto the political agenda, and have a Secretary-General of the United Nations [Kofi Annan] who, much more than anytime before, has taken AIDS health issues as part of his central agenda. World Health Organization (WHO) Director-General Gro Harlem Brundtland in an interview with National Public Radio’s “All Things Considered.” In addition to commenting about her August 2002 announcement that she would not seek a second term, Brundtland stressed that the WHO must strive to be a center of excellence and an objective source of the best information and best practices in support of member countries. Elected Director-General in May 1998, Brundtland is credited with advancing an ambitious global health agenda—especially around anti-smoking, HIV/AIDS, and tuberculosis.