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IAPAC

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Retro Part 1: A suite of new therapies (or, my funny valentine)

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Retro Part 1: A suite of new therapies (or, my funny valentine)

Mark Mascolini

Pretest for Part 1 of the 10th CROI review:

1. When was the antiretroviral pipeline fuller?
(a) 1993 (b) 2003

2. How does siRNA work?
(a) by binding to and blocking RNA (b) by binding to and shredding RNA (c) either

3. Which nonnucleoside came out in front in 2NN?
(a) nevirapine (b) efavirenz (c) too close to call

4. Which of the following new drug names is fake?
(a) TMC114 (b) TNX-355 (c) RO31-8959

5. Who wrote the lyrics for "My Funny Valentine"?
(a) Cole Porter (b) Lorenz Hart (c) George ("Bugs") Moran

DEPARTMENTS

IAPAC

battling complacency
advancing commitment

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Chicago, Illinois, USA

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Waging war against a weapon of mass devastation

José M. Zuniga

In late February 2003, the United Nations reduced by 480 million its 2002 estimate of global population growth—providing yet another reminder of the ongoing cataclysmic effects of the AIDS pandemic. AIDS features prominently in the revision because the United Nations predicts that this weapon of mass devastation will have killed 278 million people by 2050 and cut a correspondingly large swath into future birth rates.

The loss of life on such a scale should be reason enough for world leaders to make fighting AIDS a priority on par with the war on terrorism (and, since March 2003, the war on weapons of mass destruction). If more incentive is needed, however, we should remember that the impact of these deaths will translate into a bleak future from the perspective of global stability, economic prosperity, and the planet's overall well-being. It is a future that does not bode well for anyone, with repercussions even for those who never become infected and for areas of the world that do not, or at least do not yet, suffer the double-digit prevalence rates that prevail in many of the more affected countries of the developing world.

Yet world leaders, and not only those in the government of the United States, have not begun to treat the global fight against HIV/AIDS as a priority within the overall framework of policy setting.

The wealthier nations of the world continue to discuss the pandemic in terms of charitable activity, the giving of alms rather than an immediate concern necessitating focused and sustained attention. The difference, unfortunately, can be seen in the international AIDS relief plan that President George W. Bush announced during his January 28, 2003, State of the Union address.

Thinking of such a plan as a "step toward showing the world the great compassion of a great country," rather than as working on a vital issue that will affect every world citizen, is unfortunate because it encourages policy actions that may be fleeting, and delimited by unrelated political concerns. The danger is that potential global funding risks being considered a luxury afforded by charitably minded nations, rather than a necessity of sound foreign policy.

Thus, the Bush Administration, for example, came through with an international AIDS relief plan that fell short in many of its details. The proposed budget for the first year was greatly reduced and seemed to move funds from other important global health initiatives (such as immunizations for children). It made significant concessions to the pharmaceutical lobby by refusing to pledge that funding would go to cost-effective generic drugs whenever possible. There is serious discussion of requiring that recipient organizations operate entirely separately from facilities providing legal abortions, a stipulation that would inject an unrelated political issue into the plan and greatly limit its effectiveness. Legislation currently making its way through the US Congress would correct most of these problems, but what form the final version of the AIDS relief plan takes remains to be seen.

The United States is hardly the only nation that has failed to give the fight against AIDS the high priority it deserves. There is no excuse for the fact that the world's more affluent countries, *in toto*, have mustered such little global nerve and commitment to fighting the pandemic that precedent-setting initiatives such as the Global Fund to Fight AIDS, Tuberculosis, and Malaria teeter daily on the brink of bankruptcy and dissolution. One fears that this will remain the case if the parameters of policy debate are not expanded to include HIV as a threat to human security akin to terrorism and the proliferation of weapons of mass destruction.

Yet the small group of more affluent nations that account for the lion's share of global productivity and wealth are not alone in carrying responsibility for current levels of political and financial commitment to fighting this shared global burden. It is equally unacceptable that countries such as Malawi and South Africa—nations that currently face the worst horrors of AIDS morbidity and mortality—are only now taking tentative steps toward any real national response to their extremely high prevalence rates. It is equally dumbfounding, and frightening, given the United Nation's new population growth estimates, that many Indian officials deny there is a problem, while the Russian government spends more money in a year in paltry donations to international efforts than it does in fighting its own HIV and tuberculosis epidemics.

If the world community as a whole saw AIDS for the imminent threat to humanity that it is, and responded with commensurate action, such inattention would be unthinkable. When we realize the threat inherent in a disease that is expected to cause 278 million deaths within the next 50 years (46 million in the next 10 years alone), and when we understand that HIV and its effects know and respect no borders, there is no other reasonable conclusion than that our response cannot be a limited one. ■

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

UPDATE

IAPAC's Johannesburg office renamed to reflect Africa-wide activity

Reflecting the expanded initiative and geographical base of the work accomplished by the International Association of Physicians in AIDS Care (IAPAC) Southern Africa Regional Office in Johannesburg, the Executive Committee of the IAPAC Board of Trustees recently voted to rename the office as the IAPAC African Regional Office (IAPAC-AFRO).

"We are pleased that our activities are bringing us to places as far from South Africa as Kenya and Uganda," said Mulamba Diese, IAPAC-AFRO's Executive Director. "But these countries lie outside of the southern Africa region. We needed to change our name to better describe what we do. This is particularly true given that our work in the other areas of Africa is only going to increase."

Through early 2003, IAPAC's Johannesburg staff has trained more than 12,000 physicians and allied healthcare workers in the use of Diflucan and in prophylaxis and management of opportunistic infections, as the exclusive training partner in Pfizer's Diflucan Partnership Program (DPP). In 2003, IAPAC-AFRO will greatly expand these efforts, conducting training workshops in 23 African countries.

Mulamba Diese

IAPAC-AFRO is developing its continent-wide presence in other ways as well, including training of HIV-treating physicians through IAPAC's Global AIDS Learning & Evaluation Network (GALEN), creating an Africa-specific information resource center that will be available on-line to help in the fight against HIV/AIDS, expanding the I-Med Exchange Internet-based physician training program, and exploring partnerships with government and industry in all regions to expand medical education efforts.

Speaking from IAPAC's Headquarters in Chicago, President/CEO José M. Zuniga stated that by helping to improve healthcare professionals' capacity to treat patients with HIV/AIDS, IAPAC-AFRO is making an important contribution to the fight against AIDS-related morbidity and mortality.

Zuniga added that the expansion of the Johannesburg office bodes well for IAPAC's ever-growing global activities.

"With dedicated staff on the ground in strategic locations to work with our members around the world, IAPAC's ability to work toward its mission of improving the medical care of all HIV-infected people is greatly increased," Zuniga explained. "We are pleased to be working toward the growth of our European Regional Office (IAPAC-EURO) and the establishment of other regional offices." ■

IAPAC Headquarters welcomes new staff

The International Association of Physicians in AIDS Care (IAPAC) Headquarters office in Chicago welcomed two new staff additions in March 2003. According to IAPAC Vice President/Chief of Staff Michael S. Glass, these additions will strengthen the association's day-to-day operations as well as support a planned expansion of medical education initiatives.

Catherine Supina joined IAPAC as Director of Operations, with a responsibility for tracking operations across the entire association—including IAPAC's offices in Chicago, Johannesburg, and Paris. Prior to joining IAPAC, Supina worked as Personnel Manager with Integrated Genomics, Inc.

Joining IAPAC as Associate Director of Medical Education, Brooke Smith is responsible for coordinating medical education publications and symposia in North America and Europe, as well as facilitating progress around the development of Global AIDS Learning & Evaluation Network (GALEN) training modules. Smith previously worked as Project Coordinator of the Women's Interagency HIV Study (WIHS) at Northwestern University.

"IAPAC's staffing structure is expanding to meet the increasing number of initiatives advanced by the association in several geographical regions," Glass explained. "Through these staff additions, IAPAC's Senior Management is also planning for future growth—to include the establishment of additional regional offices beyond Johannesburg and Paris, and at least two technical annexes in cities of strategic importance to IAPAC."

According to Glass, IAPAC will make a major announcement in the coming month regarding a technical annex in Geneva. ■

PERSPECTIVE

Testing for competence in HIV care

John G. Bartlett

There is now a well-justified interest in rapid introduction of modern therapeutics for HIV-infected patients in resource-limited regions of the world. One of the major issues with this new effort concerns the adequacy of the medical infrastructure and the ability of the treatment force to supervise care. Based on documented benefit in the Western world—measured in terms of reduced mortality, frequency of hospitalization, frequency of AIDS-defining diagnoses, cost of care, and adherence to guidelines—we know that expertise is an important factor for successful HIV care. In fact, there is for HIV/AIDS a better-documented correlation between expertise and outcome than for any other disease. It is also clear that medical care historically has been "local" and must be done in a fashion in which local healthcare workers are in charge. Thus, it is imperative that local healthcare workers are empowered with HIV expertise.

Competencies in medical care include: patient care experience, medical knowledge, ability to transform scientific evidence to clinical decisions, communication skills, and professionalism. In general, these attributes include experience in clinical care, the ability to translate scientific observations into clinical decisions, and a record of high professional standards.

Equally important is performance on a written examination of medical knowledge and judgment. This is true for every specialty of medicine, and so it is with HIV care in resource-limited settings. The purpose of this "Perspectives" editorial is to define the guiding principles behind an International Association of Physicians in AIDS Care (IAPAC) proposal to deal with this issue: the certification component of the Global AIDS Learning & Evaluation Network (GALEN).

Table 1. **GALEN certification examination blueprint**

Area	*Percentage of total*	*Number of questions*
Pathogenesis of HIV Infection	2%	4
Epidemiology of HIV Disease Progression	2%	4
Prevention of HIV Transmission	3%	6
Diagnosis of HIV Infection	3%	6
Ethical Considerations in HIV Management	3%	6
Continuum of HIV Care	4%	8
Management of Sexually Transmitted Infections	10%	20
Introduction to Antiretroviral Therapy	10%	20
Antiretroviral Therapy in Resource-Limited Settings	11%	22
Management of Women with HIV	10%	20
Prophylaxis of Perinatal HIV Transmission	9%	18
Pediatric HIV Infection	9%	18
Prophylaxis and Treatment of Opportunistic Infections	10%	20
Prophylaxis and Treatment of Co-Infectious Diseases	10%	20
Palliative Care in HIV Management	4%	8
TOTAL	100%	200

First, it is important to emphasize that examination performance is only one component of establishing clinical competency. Other criteria are training, experience, and professionalism. In terms of the examination process, there are some fundamental rules of medical competency testing which are summarized here.

Who should write the examination?

Persons who have established expertise and a reputation in the field should write the examination—which justifies this function. They should be experienced practitioners, able to critically review data relevant to the examination. There needs to be inclusion of experts from the regions where examinations will be given in order to reflect local practice standards. The GALEN Certification Committee, composed of clinicians and public health experts from many distinct geographical

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Retro Part 1:

A suite of new therapies

(or, my funny valentine)

Mark Mascolini

Some 20 years ago Françoise Barré-Sinoussi spotted RNA in the biopsied lymph node of a 33-year-old man with an apparently acquired immune deficiency. Ten years after that US clinicians and researchers organized "The First National Conference on Human Retroviruses and Related Infections." And 10 years on most of those same clinicians—lacking too many of their 1993 patients and gaining too many more—gathered again for the tenth refrain of what has become the Conference on Retroviruses and Opportunistic Infections (CROI). This year's CROI (rhymes with Troy) had some novel features:

- A new site—Boston—where algid attendees ducked bone-breaking cold and necrotizing winds inside the Hynes Convention Center's cocoon of hotels, banks, and shops shilling high-end fashion or low-end food.
- A former US president, Bill Clinton, flogging himself for his HIV policy blunders and endorsing his rivalrous successor's five-year US$15 billion overseas AIDS plan.
- Closing sessions on the sweetest feast of the contemporary calendar, Valentine's Day.

This tender lovers' fete—celebrated in defiance of dark winter's remorseless slog—might seem a cruelly ironic capstone for a meeting about a lethal virus spread in bed. But, in truth, there has always been something a little sad and sinister about Valentine's Day.

Part 1 of this review on the 10th CROI looks at new antiretrovirals and new thinking—or marked turnabouts—on slowing the spread or replication of HIV. Results of the nevirapine-efavirenz study (2NN) fill a page or so. Part 2 will size up recent work on antiretroviral side effects and planned treatment interruptions.

After all, on the liturgical calendar February 14 commemorates one of two people (as with many things liturgical, there is some confusion), both named Valentinus and both slain by the Romans in the unhappy third century (by beheading or "languishing in a dungeon," depending on the source). But no apparent link has yet emerged between these Valentines and the ones traded by schoolchildren.[1] Then there was the fabled St. Valentine's Day Massacre, a Chicago gangland slaughter visited upon hirelings of George ("Bugs") Moran by triggermen allied to Al Capone. Even the most touching of Valentine ballads, "My Funny Valentine," makes its mark mainly through Lorenz Hart's rueful lyrics:

Your looks are laughable,
Unphotographable,
Yet you're my favorite work of art.

Indeed, when you look at antiretroviral art through Hart's self-mocking lens, Valentine's Day isn't a bad match. Some tries at thwarting the virus could be called pathetic (if not exactly laughable), and some of this therapy's failures *ought to be* unphotographable (though cruel science demands otherwise). But antiretrovirals—commonly abbreviated ARTs—have proved "favorite works of art" to countless individuals and vast populations.

Tracking rates of AIDS and death in nearly 10,000 EuroSIDA cohort members, Amanda Mocroft (Royal Free and University College Medical School, London) traced a continued dwindling of both endpoints through the most recent year of follow-up, 2002 [abstract 180*, see "Of cohorts and copies" below]. Reckoning "excess death rates" in Swiss people with HIV infection relative to the whole population, Bernard Hirschel (University Hospital, Geneva) learned that those with HIV (but without hepatitis C) have a lower excess death rate than successfully treated cancer patients, "a group who is able to obtain life insurance" [abstract 917a, see "Of cohorts and copies" below].

*Abstracts from the 10th CROI—and some posters—are available online at http://www.retroconference.org.

Hearts, flowers, HAART

There's another way this year's CROI at first seemed to resemble Valentine's Day—in carefree excess. One does not buy one's honey just one rose, but a dozen roses. For one's sweetie, a few well-picked bon-bons are a non-non; one needs a double-decker box of caloric bomblets. Just so, the stacks of tempting new antiretrovirals on review at CROI recalled juvenile fantasies of entrapment in a candy factory.

At the meeting's opening press conference, John Mellors (University of Pittsburgh) alerted scribes that the "pipeline of new antiretrovirals is fuller than it's been for a long time." And the riches didn't stop there. Alluring cellular (CEM15) and genetic (siRNA) strategies outlined by Mario Stevenson (University of Massachusetts, Worcester) bespoke an ever-sharpening focus on novel shortcuts to arrest the retrovirus (see the next section).

Impressed by this honest enthusiasm, and caught up in the 10th CROI anniversary spirit, this reporter thought it would be clever to compare 2003's deluxe bouquet of fresh therapies with the meager, seedy offerings of 1993. Further, a calculation of how many "new drugs" of yesteryear later won regulatory sanction seemed instructive. Entry criteria for the list were simple: at least one meeting abstract for an agent—or cellular or genetic manipulation—that constrained viral replication or boosted CD4 cells in people, other animals, or cell cultures.

As anticipated, the list for this year's conference impresses (Table 1). One could count six new protease inhibitors (PIs), four nucleosides (NRTIs), two non-nucleosides (NNRTIs), four integrase inhibitors (still not called IIs), *13* binding, fusion, or entry inhibitors—even a viral budding inhibitor—plus a suite of immune-based therapies and the aforementioned genetic *étoile du jour*, small interfering

Table 1. **Anti-HIV pipelines: CROI 1993 versus CROI 2003**

Agent	*At 1993 meeting: later approved**	*n*	*At 1993 meeting: unapproved for HIV**	*n*	*Total n*	*At 2003 meeting**	*n*
NRTI	d4T (P427) 3TC (P456)	2	FTC (P456), 935U83 (P576), PMEA (adefovir, S522), foscarnet (P440)	4	6	FTC (P550 and others), racivir (P552) DAPD (P554), SC34EK (P559)	4
PI	A-77003 (precursor to ritonavir, S265), RO31-8959 (saquinavir, P440), L-735,524 (indinavir, P418), nonpetidal inhibitors (precursors to amprenavir, P421)	4	A-80987 (S265), SC-52151 (S261), SDZ 28287 (S262), cyclopiazonic acid (S263), XM323 (S264), copper compounds (P416), Peptidomimetic inhibitors (P417), DMP323 (P420), PD 099560 and PD 107067 (L7)	10	14	RO033-4649 (S7), TMC114 (S8), GW433908 (S177 and S178), tipranavir (S179), atazanavir (P555), UIC-49003 (P604)	6
NNRTI	Nevirapine (S268) Delavirdine (P562)	2	TIBO R82150 (P438), atevirdine (P566), L-697,661 (P424)	3	5	Benzophenone analogs (S6) TMC-125 (P613)	2
Integrase inhibitor		0	Beta-conidendrol (S518)	1	1	Pyranodipyrimidines (S9), S-1360 (S140), L-870810 (S140), L-708,906 (P556)	4
Entry, binding, fusion inhibitor		0		0	0	AK602 (S10), TAK-220 (S11), UK-427,857 (S12), TNX-355 (S13), T-1249 (S14lb), T-649 (P615), enfuvirtide (T-20, P558), HIV-gp41 peptides (P560), PRO 542 (P561), AMD070 (P563), CD4-Ig fusion protein (P564), AK602 (P564a), SCH-C (P614)	13
Genetic therapies		0	Antisense oligodeoxynucleotide phosphorothioates (S526), guanosine/thymidine oligonucleotides (P588)	2	2	siRNA (small interfering RNA) (S49-52, P220-226)	1
Immune-based therapies		0	IL-2 (S301), interferon-alfa2B (P458), cyclosporine A (P583), inactivated HIV-1 depleted of gp120 (later Remune, L11), plasma rich in HIV p24 antibody (L12)	5	5	Interferon alfa-2b (S59), MV-BN-Nef vaccine (S60), ALVAC-HIV vCP1433 (S61), ALVAC-VIH 1433 + HIV lipopeptides (S62), Remune (P641), DermaVir (P642), HIV-1 Tat toxoid (P644), pTHr.HIVA (P645), BAY 50-4798 (P648), IL-2 (P649), GM-CSF (P653), tucaresol (P654), IL-4/IL-13 (P655), mycophenolate mophetil (P656)	14
Other		0	Hydroxyurea (P581), tamoxifen (as antiretroviral, P439), DDTC (P434), RO24-7429 (tat inhibitor, P440), SDZ 811 (cyclosporine derivative, S519), AICA riboside (as enhancer of ddI and ZDV, S520), D4-PE(40) (cytotoxic to HIV-infected cells, P558), GLQ223 (P560), organosilicon compound (P561), succinylated human serum albumin (P569), hypericin (St. John's wort, ACTG 150, P570), SC-48334 (alpha glucosidase I inhibitor, P574)	12	12	PA-457 (budding inhibitor, S14)	1
		8		37	**45**		**45**

*Slide (S) or poster (P) abstract numbers in parentheses.

Sources: Abstract books from the First National Conference on Human Retroviruses and Related Infections. December 12-16, 1993. Washington, DC; and the 10th Conference on Retroviruses and Opportunistic Infections. February 10-14, 2003. Boston.

RNA (siRNA). The total of vernal viral nemeses reached a lavish 45.

Then there was 1993. The list of hopefuls included some future stalwarts—lamivudine (3TC), nevirapine, and indinavir. But who, besides the presenters, remembers cyclopiazonic acid (another Merck PI), RO24-7429 (Roche's tat inhibitor), or the organosilicon compound from the University of Bordeaux? Toting up this 10-year-old list, one counts—45 vernal viral nemeses!

Of course one could argue that the 1993 roster includes some off-the-wall offerings (even back then lots of docs looked askance at infusing people with plasma rich in anti-p24 antibody) and some dandy shockers (hypericin, the prime mover in St. John's wort, studied in ACTG protocol 150). But the list also includes a few agents still hotly debated, and used, today, *viz* hydroxyurea (in a Franco Lori poster) and interleukin 2 (with Cliff Lane as the senior author). IL-2 isn't the only therapy to appear on both lists—the others are FTC, now called emtricitabine, the embattled immune stimulant Remune, and interferon alfa2B. And who's to say the failures of yore—for example, antisense—made less sense then than today's genetic pole sitter, siRNA? To be sure, many a gene therapy and antisense savant from 1993 resurfaced in 2003 espousing siRNA.

So here we are 10 years later, without the benefit of hindsight that smarty pants

of 2013 will enjoy, and the job of everyone with a stake in stopping HIV remains the same: Without passion (ardent Valentines begone), fathom the cold data coolly gathered by the world's top HIV researchers and decide which will blossom in one year or two, which will flourish as the decade matures, and which will wither neath the insensate harrow of scientific scrutiny.

STARTING ANEW (AGAIN)

Every HIV meeting worth sitting through starts with the same question: What's new? CROI's organizers give reporters a head start by stapling together a sheaf of abstracts with trenchant analyses by scientific committee members. Some of those Solons show up at a first-day press conference to construe their best-of-show picks and to twine the strands of discrete studies into signals of important change. Hence, John Mellors, as just mentioned, nudged the new-therapies bandwagon to the starting line, inviting willing reporters to push. Eyeing vaccine research and some budding benchwork, David Ho (Aaron Diamond Center, New York) and Mario Stevenson also espied possibly pivotal developments. There were three, and a fourth caught the fancy of the mainstream press:

HIV **vaccine research** began—and has continued for many a year—with attempts to summon antibodies that will neutralize a newly transmitted retrovirus. Early on, this worked well in the lab, but not on the street or in the field—breeding grounds for unimpressed "field isolates." So vaccine research reversed course, prodding troops of viral proteins to excite cell-mediated responses that would stymie HIV after infection but not prevent infection itself.

Bad news on that front, said David Ho. Daniel Barouch, working in Norman Letvin's Beth Israel Deaconess lab in Boston, reported that three of four monkeys given a vaccine that dragoons cytotoxic T lymphocytes (CTLs) against the virus had fallen sick after only three years of follow-up [abstract 76]. The infecting simian immunodeficiency virus, or SIV, had wriggled free from strong-arm CTLs through "a stereotypic pattern of viral escape." This doleful outcome does not spell the end of so-called prime-boost CTL strategies because the animals got only the priming shots and newer prime-boost medleys may prove more potent.

But this study and others, Ho commented, make it clear that "protection against disease progression may be lost with time" if one riles only cell-mediated immunity. So, it's back to antibodies, in Ho's opinion. He cited "significant progress" in finally tracking down spots on HIV's envelope that may prove vulnerable to antibody attack. "The new information," he told the press corps, "is already generating novel ideas for creating 'immunogens' that could be tested in animals for the ability to induce HIV neutralizing antibodies."

The tenth CROI had no word on one antibody vaccine—in fact, the *only* vaccine—to confront HIV in big efficacy trials, VaxGen's AIDSVAX. But that news came a few weeks later, confirming majority opinion that the gp120 vaccine would not work and rousing controversy about whether the small numbers of African Americans and Asians enrolled supported a claim that AIDSVAX may protect them.

Tufts University's John Coffin, in the first talk at the Boston gathering [abstract 1], displayed two stark and still inescapable statistics:

Number cured of HIV: <1

Number of HIV infections prevented by vaccine: <1

And, Coffin added, these null results "will probably not change for a considerable time." VaxGen later claimed that Coffin's second dictum no longer holds—in African Americans and Asians—but many demurred pending closer scrutiny of the AIDSVAX results and their statistical analysis.

If it has nothing else going for it, small interfering RNA has a sleek, digital-age moniker: **siRNA**. But, then, *antisense* and even *gene therapy* exuded linguistic cachet in their prime.

• *What is siRNA?* Small (21- to 23-base pair long) snippets of RNA can be cut from longer strands by an enzyme called dicer. These naturally occurring siRNAs hunt down and *interfere* with matching base-pair strands on messenger RNA, either by binding to and blocking the matching RNA or by shredding it. Such doings are called RNA interference (RNAi).

• *"Naturally occurring"? You mean siRNA isn't just some high-tech tool but something already floating around in people?* Right. And it's floating around in plants, too. Phillip Zamore (University of Massachusetts, Worcester) explained that RNA interference was discovered (though unnamed at the time) by a scientist trying to figure out why purple petunias kept turning white [abstract 49]. Later work showed that siRNAs can inhibit expression of the purple gene. Now, of course, the mechanism behind these naturally occurring RNA weapons *is* being turned into a high-tech tool.

• *Why do plants and animals have siRNA?* Zamore said its primary function in plants is probably antiviral. Whether this antiviral function explains why humans have siRNA remains uncertain, according to Zamore. But Harvard RNAi researcher Judy Lieberman explained this genetic trick as "an ancient evolutionarily conserved mechanism to protect the genome from damage by viruses and other insertable genetic elements" [abstract 50].

• *Can siRNA be marshaled to attack HIV?* That's the hope, and the focus of a burgeoning field of research.

• *How would it work?* Several approaches are under study. Gene therapy researcher John Rossi (City of Hope, Duarte, California) slipped siRNAs matching parts of HIV's genome into blood-producing stem cells [abstract 50]. Inside SCID-hu mice, those stem cells became T cells that resisted infection with HIV. Lieberman dispatched siRNA into macrophages, targeting both viral and cellular genes and rendering them resistant to HIV for three weeks [abstract 51]. In David Baltimore's lab at the California Institute of Technology, siRNA directed against the HIV coreceptor CCR5 inhibited infection of human T cells.[2]

• *How does siRNA get ferried into cells?* Rossi and Baltimore piggybacked siRNA on a lentivirus, a tactic that yielded "reasonably decent" expression of siRNA for Rossi. But viral vectors remain risky. Lieberman intravenously infused siRNA into mouse models of autoimmune hepatitis. More than 80 percent of their liver cells lapped up siRNA, which silenced Fas, a mediator of liver cell death. But some doubt that other cells of interest, like CD4 cells, will absorb siRNA as avidly. After all, said Bryan Cullen (Duke University, Durham,

North Carolina), the liver "exists to soak up things."

• *Besides delivery problems, what other hurdles does siRNA research face?* So far, RNA interference via transfected siRNA remains transient, Cullen [abstract 52] and the other CROI speakers warned. Rossi noted, and Cullen agreed, that single point mutations can "eliminate siRNA function."

• *Is there any way around resistance to siRNA?* Cullen suggested that simultaneously deploying multiple siRNAs aimed at highly conserved regions of the viral genome may build an insurmountable barrier to resistance. Or targeting a "critical, and invariant, cellular cofactor" may do the trick.

• *Do such targets exist?* CCR5, a target studied by Baltimore and Lieberman, may be one. Besides being essential for infection with CCR5-tropic HIV, Cullen reminded attendees, CCR5 "is entirely dispensable for human well-being." And early evidence suggests that siRNA can block both CCR5 expression and CCR5-dependent HIV infection—in cell culture.

Here's an amazing tale. "Because of proteins like **APOBEC**," according to Mario Stevenson, "humans are innately resistant to infection by viruses like HIV." So what goes wrong? Most human cells carry an APOBEC protein called **CEM15**, which slams the door on HIV replication. But HIV, never at a loss, has a gene whose sole function seems to be knocking out CEM15. The gene is ***vif***, the appropriately named viral infectivity factor.

Michael Malim (King's College, London) amplified on this classic tug of war in a plenary talk [abstract 5]. The *vif* gene and its protein product Vif, he explained, show up in most lentiviruses and in *all* mammalian lentiviruses, such as HIV-1, HIV-2, SIV, and FIV. Vif makes budding virions infectious. Without Vif, virions still bud from infected cells, but they can't infect fresh cells. Malim offered some details:

- All human tissues studied, except brain, express CEM15.
- CEM15 may disrupt genomic or cellular RNA, causing slipshod assembly of new virions.
- Turning on CEM15 in cells that normally lack the protein inhibits infectivity and replication of viruses lacking *vif*.
- CEM15 has perhaps eight cousins. These other "RNA-editing enzymes" play crucial roles such as spurring antibody diversification and sparking metabolism of low-density lipoprotein cholesterol.

To get a better handle on how APOBEC/CEM15 stymies HIV, Roberto Mariani and colleagues at the Salk Institute in La Jolla tracked the action of this protein's mouse equivalent [abstract 72]. They found it in lymphoid tissues including spleen, thymus, and lymph nodes, and in heart and lung. Mouse APOBEC shut down HIV replication even better than human APOBEC. As little as 1 ng, the Salk team learned, "effectively blocked HIV-1 infectivity." And HIV-1 Vif failed to reverse this action unless APOBEC levels were low.

Can science exploit CEM15's innate antiviral moxie in humans? It should be "considered," Malim opined, but it won't be easy. Eviscerating *vif* may be preferable to boosting CEM15, because this protein's panoply of activities remains poorly understood. In animal models, Malim noted, meddling with CEM15 makes tumors grow.

Can you fight a virus with a virus? If one is **GBV-C** and the other **HIV-1**, the answer may be yes. GBV-C, once labeled hepatitis G virus, turned out not to cause hepatitis or any other known disease. But when GBV-C actively replicates in people infected with HIV, it seems to blunt HIV's virulence. If a GBV-C-infected person clears that virus, however, HIV runs amok.

Studying 230 people with HIV infection, Per Björkman (Malmö University Hospital, Sweden) found that harboring active GBV-C at HIV diagnosis does not affect progression to AIDS or death [abstract 157]. But the viruses seem to interact. Whereas two of 31 people (6 percent) who had AIDS when diagnosed with HIV also had GBV-C in their blood, 54 of 175 (31 percent) diagnosed with asymptomatic HIV disease carried GBV-C ($P = 0.008$).

During a median 4.33 years of follow-up, 11 of 44 people originally infected with GBV-C cleared that virus without evidence of GBV-C antibody seroconversion. Compared with others in the study, those people had:

- A higher death rate: eight of 11 (73 percent) versus 16 of 89 (18 percent) ($P = 0.007$)
- A higher AIDS incidence: 10 of 11 (91 percent) versus 19 of 70 (27 percent) ($P < 0.001$)
- A faster drop in CD4 cells: 145 versus 56 cells/mm^3 yearly ($P = 0.006$)

Scrutinizing stored plasma samples from gay men enrolled in the Multicenter AIDS Cohort Study (MACS), Carolyn Williams (National Institute of Allergy and Infectious Diseases, Bethesda) and MACS colleagues confirmed two of Björkman's findings: Early GBV-C status does not affect survival (after five to six years in this study). And clearing GBV-C has nasty consequences [abstract 159lb].

Williams found that GBV-C status at the five- to six-year follow-up visit had a dramatic impact on mortality. Compared with men who had circulating GBV-C at both visits:

- Those without GBV-C at either visit were 2.43 times more likely to die ($P < 0.001$)
- Those who cleared GBV-C between visits were 5.87 times more likely to die ($P < 0.001$)

Men with GBV-C viremia at both visits lost an average 26 CD4 cells/mm^3 yearly; men negative for GBV-C at both visits lost 37 cells/mm^3 yearly; and men who cleared GBV-C between visits lost 107 cells/mm^3 yearly. These three groups did not differ in median duration of follow-up, date of seroconversion, antiretroviral use, median HIV load, or prevalence of the protective CCR5 delta32 mutation.

What's the link between GBV-C and HIV? Coreceptors and chemokines, according to a cell study by Jack Stapleton (University of Iowa, Iowa City) [abstract 156]. He found curtailed expression of the HIV coreceptors CCR5 and CXCR4 on peripheral blood mononuclear cells (PBMCs) exposed to GBV-C isolates or infectious clones. Inhibition of HIV replication in these cells required ongoing GBV-C replication. Compared with mock-infected PBMCs, cells spiked with GBV-C produced more of the cytokines IL-2 and IL-8 and more of the chemokines MIP-1 alpha, MIP-1 beta, SDF-1, and RANTES.

Stapleton believes results of his experiments and the two cohort studies mean GBV-C infection may have "a direct inhibitory effect" on HIV replication. The Swedes aren't so sure. They suggest that "GBV-C status in HIV-1 infection is probably a secondary phenomenon during disease progression rather than an independent prognostic factor." But Stapleton thinks researchers should even consider injecting GBV-C into people already burdened by HIV.[3] Yet the notion of exposing people to a virus discovered only nine years ago—even though it seems innocuous now—sounds scary to some, because the immune system could not be allowed to clear GBV-C. All three studies suggest that, once infected with GBV-C, getting rid of that virus would be worse than never having it at all.

Table 2. **First-line nevirapine versus efavirenz after 48 weeks**

		Failure		
	Success (%)	*Drug change (%)*	*Virologic* (%)*	*Progression (%)*
Nevirapine once daily	56.4	29.1	11.4	3.1
Nevirapine twice daily	56.3	22.0	18.9	2.8
Efavirenz	62.3†	20.0	15.3	2.4
Nevirapine/efavirenz	46.9†	34.5	16.3	2.3

	Less than 50 copies/mL	
	Intent-to-treat analysis (%)*	*On-treatment analysis (%)*
Nevirapine once daily	70.0	88.7
Nevirapine twice daily	65.4	81.5
Efavirenz	70.0	86.8
Nevirapine/efavirenz	62.7	79.5

*Missing-data-equal-failure analysis.
† Only significant difference ($P < 0.001$).

Source: Joep Lange, abstract 176.

NO LACK OF NEW DRUGS

Only a few years ago, drug industry merger mania occasioned concern over the future of antiretroviral development. How many HIV drugs could one reasonably expect from one company where once there had been two, three, or even four? Indeed, one heard nothing at the 10th CROI about the second-generation NNRTIs once being developed by DuPont but now the property of Bristol-Myers Squibb. And if GlaxoSmithKline buys Bristol-Myers Squibb, what then? Yet the bleakest versions of this doomsday scenario remain dark imaginings. Instead, old hands long absent from the fray (Pfizer, Schering-Plough) and fresh faces with new wares (Tanox, Panacos) peopled the new antiretroviral slide session and poster boards.

But wait. Before auditioning CROI's cavalcade of new candidates, consider two mainstays of the antiretroviral repertoire—nevirapine and efavirenz—on stage together for the first time. Well, at least for the first time in a big, multicontinental, randomized trial: 2NN.

Who won 2NN? You

Before there was 2NN, the 1,216-person head-to-head showdown between nevirapine and efavirenz, there was SENC, the Spanish Efavirenz-Nevirapine Comparison trial, which also randomized treatment-naive people to begin one or the other NNRTI plus two nucleosides.[4] This little-noted trial differed from 2NN in two important ways: it enrolled only 67 people, and it excluded people with viral loads above 100,000 copies/mL. After 48 weeks SENC's intent-to-treat analysis determined that 64 percent assigned to nevirapine and 74 percent to efavirenz had a viral load under 50 copies/mL. But that difference lacked statistical significance. The authors appropriately noted that such a difference may have emerged in a bigger trial.

2NN was 18 times bigger than SENC, and nevirapine still kept statistical pace with efavirenz through 48 weeks, even among people who began treatment with a viral load above 100,000 copies/mL. Joep Lange, who heads the IATEC trials group at the University of Amsterdam, and IATEC's Frank van Leth spelled out the details in a slide talk [abstract 176] and poster [abstract 752].

Lange and colleagues on six continents randomized untreated adults to take stavudine (d4T) and 3TC plus 400 mg of nevirapine once daily, 200 mg of nevirapine twice daily, standard once-daily efavirenz, or nevirapine plus efavirenz at 400/800 mg once daily. About 400 people got assigned to arms two and three to ensure statistical power to discriminate between those standard doses, while about 200 got assigned to the unconventional dosage arms, one and four. Baseline traits matched well from arm to arm, with (for all groups) 63 percent men, a median age of 34 years, a median CD4 count of 190 cells/mm^3 (range 70 to 330 cells/mm^3), and a median viral load of 4.7 logs (range 4.4 to 5.5 logs). Equivalent proportions had hepatitis B virus (HBV) coinfection (5.3 percent overall) or hepatitis C virus (HCV) coinfection (9.5 percent overall).

The researchers defined failure by four criteria:

- Less than a 1-log viral load drop by week 12
- Two consecutive viral loads above 50 copies/mL from week 24 on
- A new AIDS diagnosis or death
- A change in assigned treatment

A week 48 missing-data-equal-failure analysis found a significant response difference only between the efavirenz arm and the nevirapine/efavirenz arm (Table 2). Nor did the single-nevirapine arms differ from the single-efavirenz arm in intent-to-treat or on-treatment analyses of proportions with viral loads below 50 copies/mL at 48 weeks. For people starting therapy with a viral load above 100,000 copies/mL, those taking efavirenz met the trial's success criteria slightly more often (61.3 percent) than those taking nevirapine/efavirenz (57.1 percent), twice-daily nevirapine (57.3 percent), or once-daily nevirapine (51.5 percent), but between-arm differences fell shy of statistical significance. CD4 gains proved equivalent across arms.

The 2NN team did tease out some differences in side effect rates. Grade 3 or 4 hepatobiliary side effects trended higher in the twice-daily (2.6 percent) and once-daily (1.8 percent) nevirapine groups than in the double-NNRTI arm (1.0 percent) or the efavirenz arm (0.5 percent) ($P = 0.082$ across arms). Clinical hepatitis also cropped up more in the nevirapine groups (2.1 and 1.4 percent) than with nevirapine/efavirenz

(1.0 percent) or efavirenz (0.3 percent), but these differences lacked statistical significance. (One woman without evidence of HBV or HCV coinfection died of hepatitis while taking nevirapine.) The once-daily nevirapine group had a significantly higher rate of grade 3 or 4 hepatobiliary lab toxicities (13.2 percent) than did the efavirenz arm (4.5 percent, $P < 0.001$), the only significant between-arm difference in lab markers. Clearly, though, liver toxicity was rare by any measure in any study arm.

Grade 3 or 4 rash proved more common with once-daily (4.1 percent) and twice-daily (3.1 percent) nevirapine than with efavirenz (1.8 percent), though again these differences lacked statistical significance. (A man taking nevirapine died of septicemia while recovering in the hospital from Stevens-Johnson syndrome.) Grade 3 or 4 central nervous system or psychiatric side effects troubled more people in the efavirenz arms (5.7 percent with nevirapine/efavirenz and 5.5 percent with efavirenz) than in the nevirapine arms (3.6 percent twice daily and 1.4 percent once daily) ($P = 0.001$ across arms).

The bottom line in the toxicity match-ups is a distinct disadvantage for nevirapine/efavirenz, with 29.7 percent in that group stopping therapy temporarily or permanently for any side effect, compared with 24.1 percent for once-daily nevirapine, 21.2 percent for twice-daily nevirapine, and 15.5 percent for efavirenz ($P < 0.001$ across arms). Are those differences between the single-nevirapine arms and the single-efavirenz arm statistically significant? By the strictest interpretation, Frank van Leth told *IAPAC Monthly*, the answer is no. Blunt pairwise comparisons between the once-daily and twice-daily nevirapine arms and the efavirenz arm did suggest significantly more dropouts with nevirapine ($P = 0.009$ once-daily versus efavirenz and $P = 0.039$ twice-daily versus efavirenz). But after statisticians scrupulously adjusted those figures to account for multiple testing in four preplanned comparison arms, the only significant difference remained between efavirenz and nevirapine/efavirenz.

This is probably more than most readers want to know—or *need* to know—about side effect statistics. As so often proves true when statistical hair-splitting requires electron microscopy to discern differences, the proper question becomes not "Are these differences statistically significant?" but "Are these differences clinically meaningful?" Most seasoned HIV clinicians will be content to walk away from 2NN with the primary endpoint message—equivalent failure rates in the three single-NNRTI arms and more failures with the more toxic double-NNRTI tactic. From there, picking between these two drugs for first-line regimens will not be a roll of the dice, but an already set appreciation of corollary risks and benefits.

Among nevirapine's possible benefits, earlier work suggested, may be its effect on lipids. 2NN confirmed findings of an Atlantic trial substudy that saw an apparently antiatherogenic profile with nevirapine but not with indinavir.[5] Considering only people who stayed with their assigned 2NN regimen for 48 weeks and lumping the two nevirapine arms to compare them with the single efavirenz group, van Leth charted three significant benefits for nevirapine [abstract 752]:

- Larger increase in cardioprotective high-density lipoprotein cholesterol (HDL-C) ($P < 0.001$)
- Larger decrease in total cholesterol to HDL-C ratio ($P < 0.001$)
- Smaller increase in triglycerides ($P = 0.01$)

Whereas the total-to-HDL-C ratio stayed fairly flat among people taking efavirenz (5.9 at baseline and 6.3 at week 48), it narrowed with nevirapine (5.3 at baseline and 4.5 at week 48).

Again, the savvy clinician will ask whether these statistically significant lipid differences translate into clinical benefit. The context is complicated—a chronic disease that will require treatment for two, three, or more decades with drugs that will be as different 10 years from now as today's best antiretrovirals are from 1993's crop. Add to that the still-muzzy datastream from cohort studies metering antiretroviral fallout on cardiovascular quiddities.

For now, 2NN confirms what many prescribers have long sensed: In the peerless treatment-naive person with world-class liver function, no propensity to rash, zero cardiovascular risk factors, exemplary psyche scores, and a fondness for vivid dreams, nevirapine and efavirenz are both swell picks. If you see imperfect patients, more thought will be needed. On average, nevirapine looks more inclined to cause rashes and is more hepatotoxic. Careful liver function monitoring guidelines are on the books for people starting this drug.[6] Efavirenz can play mean tricks on the central nervous system, and it's a bad choice for women who may become pregnant. And, oh yes, nevirapine costs less.

Atazanavir at 108 weeks, and after nelfinavir

Researchers are still puzzling through the poor results of the atazanavir-versus-efavirenz trial presented last year.[7] A 48-week intent-to-treat analysis of that multinational study counted only 32 percent of treatment-naive people randomized to atazanavir with a viral load under 50 copies/mL, and only 37 percent assigned to efavirenz reached that mark. The trial's official conclusion underlined atazanavir's "equivalence" with efavirenz. But at the Retrovirus meeting Martin Hirsch (Massachusetts General Hospital, Boston) [abstract 187] called that analysis "difficult to reconcile" with results of an atazanavir-versus-nelfinavir trial in treatment-naive people, which also showed 48-week virologic equivalence.[8] Yet nelfinavir did not keep pace with efavirenz in a study Hirsch planned, ACTG 384,[9] and no one would consider nelfinavir today's standard of comparison for the phase III trial of a new drug.

The 2NN results (preceding section) contradict the poor showing of efavirenz in the atazanavir-efavirenz trial and confirm earlier studies, like ACTG 384, attesting to this NNRTI's antiviral vigor. Even though 2NN, like the atazanavir-efavirenz study, counted consecutive viral loads above 50 copies/mL as a virologic failure, the 48-week intent-to-treat rate of sub-50-copy responses measured 70 percent with efavirenz (as well as with once-daily nevirapine). But atazanavir scored some virologic points at CROI in a long-term analysis of the atazanavir-nelfinavir trial.

After 48 weeks of random assignment to atazanavir or nelfinavir (plus d4T/3TC), study participants could continue one of the two atazanavir doses (400 or 600 mg once daily) or switch from nelfinavir to 400 mg of atazanavir [abstract 555]. Robert Murphy (Northwestern University, Chicago) reported that 63 people made the switch, while 283 continued atazanavir. At the switch point 70 percent in the nelfinavir-to-atazanavir arm had a viral load below 400 copies/mL, and 48 percent had fewer than 50 copies/mL. After 24 weeks on

atazanavir those rates improved to 86 percent under 400 copies/mL and 59 percent under 50 copies/mL. No one in the switch arm stopped atazanavir because of treatment failure. At 108 weeks after randomization in the initial study, an intent-to-treat analysis counted 51 percent in the 600-mg atazanavir arm, 47 percent in the continuous 400-mg arm, and 49 percent in the nelfinavir-to-atazanavir arm with a viral load under 50 copies/mL.

People who continued atazanavir in the extension study had little change from initial baseline levels of total cholesterol, ominous low-density lipoprotein cholesterol (LDL-C), or triglycerides. HDL-C rose from 40 mg/dL at baseline to 46 mg/dL at week 48 of the first study and stayed there for another 24 weeks of atazanavir. People who traded nelfinavir for atazanavir enjoyed four significant lipid benefits 12 weeks after the switch:

- 16 percent drop in total cholesterol ($P < 0.0001$)
- 21 percent drop in fasting LDL-C ($P < 0.0001$)
- 28 percent drop in fasting triglycerides ($P < 0.0001$)
- 5 percent gain in HDL-C ($P < 0.05$)

For total cholesterol, LDL-C, and triglycerides, the significant improvements held through another 12 weeks. About 10 percent in each study arm had clinician-reported lipodystrophy, while 26 percent taking continuous 400-mg atazanavir, 44 percent taking continuous 600-mg atazanavir, and 13 percent switching from nelfinavir to atazanavir had grade 3 or 4 bilirubin elevations. Respective jaundice rates were 3 percent, 3 percent, and 6 percent.

Fosamprenavir: first line or later?

As with atazanavir, US Food and Drug Administration (FDA) analysts are even now threshing through trial data on another PI, GlaxoSmithKline's GW433908, the amprenavir prodrug (fosamprenavir) also called 908. CROI attendees scanned an ample load of those data in two slide talks, one involving a comparison with nelfinavir in treatment-naive people and one pitting ritonavir-boosted 908 against lopinavir in people with PI experience. The GlaxoSmithKline PI shares at least one trait with rival atazanavir: It can be taken once daily (but only when boosted by ritonavir). Unlike atazanavir, 908 outdistanced twice-daily nelfinavir in treatment-naive people. But it may lag lopinavir as a second- or third-line PI.

Table 3. **GW433908/r versus lopinavir/r at 24 weeks after one or two PIs**

	908/r once daily	*908/r twice daily*	*Lopinavir/r*
Mean AAUCMB (log)	-1.48	-1.50	-1.66
<400 copies/mL* (%)	58	60	69
<50 copies/mL* (%)	40	42	48
CD4+ change (%)	+72	+62	+63

*Intent-to-treat analysis.
AAUCMB = time-averaged viral load change from baseline.
Source: Edwin DeJesus, abstract 178.

The naive trial randomized 251 people in a 2-to-1 ratio to 1,400 mg of 908 or 1,250 mg of nelfinavir twice daily [abstract 177]. Everyone also took abacavir and 3TC. Though most study participants lived in the US ($n = 153$), sizable proportions signed up in Panama ($n = 52$), Puerto Rico ($n = 25$), and South Africa ($n = 21$). About one third were women. The median baseline viral load measured a little over 4.8 logs (about 63,000 copies/mL) in both treatment groups, and more than 40 percent in both groups had a viral load above 100,000 copies/mL. The median CD4 count stood at 214 cells/mm^3 in the 908 arm and 212 cells/mm^3 in the nelfinavir arm, and close to half had fewer than 200 cells/mm^3.

After 48 weeks 66 percent taking 908 and 51 percent taking nelfinavir reached the primary endpoint, a viral load below 400 copies/mL in an analysis that defined failure as never going below 400 copies/mL, rebounding from below 400 copies/mL, or stopping treatment. Jeffrey Nadler (University of South Florida College of Medicine, Tampa) did not report whether this (or any) difference reached statistical significance. By the same type of analysis, 55 percent taking 908 and 41 percent taking nelfinavir had a 48-week viral load below 50 copies/mL. In the 908 arm nearly equal proportions starting treatment above or below the 100,000-copy mark reached a sub-50 viral load. Not so in the nelfinavir group, where 54 percent starting below 100,000 copies/mL ended up under 50 copies/mL compared with 24 percent starting above 100,000 copies/mL. The median CD4-cell gain measured 201 cells/mm^3 with 908 and 216 cells/mm^3 with nelfinavir.

Side effect rates proved similar in the two groups, except that 18 percent taking nelfinavir versus 5 percent taking 908 endured diarrhea ($P = 0.002$). While 9 percent taking 908 had a hypersensitivity reaction or rash, 5 percent taking nelfinavir did, a nonsignificant difference. Mean fasting triglycerides and total-to-HDL-C ratio were below US National Cholesterol Education Program cutoffs (200 mg/dL and 6.5) in both treatment groups.

The second 908 study randomized 320 people who had taken one or two PIs (a handful had taken more) to genotype-selected NRTIs (usually including tenofovir) plus 908/ritonavir (1,400/200 mg once daily or 700/100 mg twice daily) or standard-dose lopinavir [abstract 178]. No one could take a nonnucleoside. Median baseline viral loads stood over 4.1 logs (about 12,500 copies/mL), and the median starting CD4 count was 263 cells/mm^3.

The study's primary endpoint is time-averaged change in viral load from baseline (AAUCMB) at 48 weeks. The trial lacks the power to show statistically significant between-group differences in rates of sub-50 or sub-400 viral loads. Edwin DeJesus (Infectious Disease Clinic, Altamonte Springs, Florida) reported 24-week findings, which did not include a reckoning of statistical significance for AAUCMB. At 24 weeks the numbers showed "noninferiority" of either 908 arm to lopinavir, although virologic trends all ran in lopinavir's favor (Table 3).

Some attendees wondered whether AAUCMB is the best endpoint for a study population like this. Such an area-under-the-curve calculation makes sense for study groups with highly drug-resistant virus and faint chance of reaching a viral load under 50 copies/mL, explained session cochair Julio Montaner (University of British Columbia). But because

respectable proportions in this trial *did* notch sub-50 loads (Table 3), AAUCMB may not be the most telling yardstick. Another way to size up 908 in PI-experienced people would be to chart virologic responses against baseline resistance mutations and viral susceptibility. DeJesus said that analysis will come with the 48-week results. Fewer people taking once-daily 908 (19 percent) than twice-daily 908 (35 percent) or lopinavir (34 percent) had a grade 2 to 4 side effect.

Whether this amprenavir prodrug can find a following as an unboosted or a boosted first-line agent, or a boosted rescue PI, cannot be surmised from findings so far. What can be said is that boosted 908 given to treatment-naive people spawned no protease mutations, while unboosted 908 did [abstract 598]. This analysis, presented by GlaxoSmithkline's Sarah Macmanus, involved people with consecutive viral loads above 1,000 copies/mL in two 908 studies—the nelfinavir comparison outlined by Jeffrey Nadler (above) and a contest between once-daily 908/ritonavir (1,400/200 mg) and twice-daily nelfinavir, both with abacavir and 3TC. Comparing baseline genotypes with on-therapy genotypes during viral rebounds, Macmanus consistently mapped more protease and nucleoside mutations in Nadler's unboosted 908 group:

- New primary or secondary protease mutation: 8 of 29 (28 percent) unboosted versus 0 of 32 boosted
- New 3TC mutation: 16 of 29 (55 percent) unboosted versus 4 of 32 (13 percent) boosted
- New 3TC or abacavir mutation: 16 of 29 (55 percent) unboosted versus 4 of 32 (13 percent) boosted

The GlaxoSmithKline team suggested the results support using boosted 908 as "first-line [therapy] or early in the treatment continuum."

Tipranavir: hare-raising comparison

The much-heralded PI tipranavir had a head start over atazanavir and 908 in the race to regulatory sanction. But it became the laggard hare in this marathon, only recently reaching the phase III leg because of difficulties defining the best dose and delays due to a shift in developers. A phase II trial detailed by Joseph Gathe (Therapeutic Concepts, Houston) confirmed tipranavir's activity against virus laden with some infamous protease mutations [abstracts 179 and 596].

Table 4. **FTC versus d4T after 48 weeks in treatment-naive people**

	FTC (n = 286)	*d4T (n = 285)*	*P*
<50 copies/mL (%) (NC = F*)	74.2	58.0	<0.0001
Virologic failure† (%)	5.3	12.7	<0.01
Efficacy failure‡ (%)	9.4	17.9	<0.01
CD4+ gain (cells/mm^3)	153	119	<0.05
Kaplan-Meier probability of time to loss of virologic response	22.4	41.8	<0.001
Kaplan-Meier probability of time to tolerability failure¶	7.4	15.4	0.0028

*Noncompleter-equals-failure analysis. All study participants also took ddI and efavirenz.
† Never <400 copies/mL or consecutive rebounds above 400 copies/mL.
‡Virologic failure, disease progression, death, or loss to follow-up.
¶ Permanent discontinuation because of death or toxicity.
Source: Pedro Cahn, abstract 606.

Because the study aimed to pick the phase III dose of tipranavir in a cohort with treatment experience, the primary endpoints were viral load drop at two weeks (before other drugs in the regimen could be changed) and side effects at four weeks. Study entry thresholds included treatment with all three antiretroviral classes and one or more mutations at protease sites 30, 46, 48, 50, 82, 84, and 90. Researchers randomized 216 people to one of three twice-daily tipranavir/ritonavir doses: 500/100 mg, 500/200 mg, or 750/200 mg. The median starting CD4 count stood at 153 cell/mm^3 and the median viral load at 4.53 logs (about 33,900 copies/mL).

Whereas half the people assigned to 500/100 mg failed to hit a target trough concentration above 20 µM, more than three quarters in the other two arms did. By a last-observation-carried-forward analysis, week-two viral load drops measured 0.87 log with 500/100 mg, 0.97 log with 500/200 mg, and 1.18 logs with 750/200 mg; differences between arms lacked statistical significance. Boehringer Ingelheim, tipranavir's developer, chose the 500/200-mg dose for phase III studies because it yielded better troughs than 500/100 mg, with less interpatient variability than 750/200 mg. Fewer people taking 500/200 mg than 750/200 mg had to suspend treatment because of side effects. Gathe reported that 12.5 percent taking 500/200 mg and 16.9 percent taking 750/200 mg had one or more severe side effects. Overall, about 15 percent suffered grade 2 diarrhea and 12 percent vomiting.

Genotypic analysis focused on four changes that Boehringer Ingelheim calls universal PI-associated mutations or UPAMs—L33I/V/F, V82A/F/L/T, I84V, and L90M. Virus with one or two UPAMs at baseline hardly tarnished susceptibility to tipranavir but proved resistant to other PIs. Two UPAMs, for example, yielded a median 1.3-fold change in tipranavir IC_{50} (50 percent inhibitory concentration) relative to wild-type virus, compared with a 9.6-fold change for saquinavir, 13.1-fold for amprenavir, 21.1-fold for indinavir, 32.8-fold for nelfinavir, 79.6-fold for lopinavir, and 97.9-fold for ritonavir. Only people with three UPAMs, and as many as 16 to 20 mutations in all, had more than a 2-fold change in susceptibility to tipranavir.

A 2-fold change in IC_{50} may mark the cutoff for virologic response to tipranavir, the researchers propose. Across the three study arms, the median viral load fell over 1 log in people with a 1- to 2-fold change in viral susceptibility to tipranavir. But responses nose-dived to a median 0.2 log or less when virus had a 2- to 4-fold change in susceptibility. Yet even in this PI-experienced population (93 percent had more than 10 protease mutations at baseline), 69 percent began the study with less than a 2-fold change in IC_{50} to tipranavir.

FTC: once-daily mate for tenofovir?

Although the once-a-day nucleoside emtricitabine (FTC) did not earn a slide slot at the 10th CROI, four posters sated the inquisitive. Interest in this long-studied drug leapt a quantum or two when Gilead bought its developer, Triangle. This union raised the winsome possibility of a once-daily double nuke in a single pill—FTC and tenofovir—heady competition for twice-daily Combivir (ZDV/3TC).

The longest FTC study presented, by Triangle's Charles Wakeford, involved

215 people originally randomized to take FTC (200 mg once daily) in a 48-week comparison with continued 3TC [abstract 550]. All 215 had a viral load under 400 copies/mL at week 48 and agreed to continue FTC in an extension study, along with 74 other people. A Kaplan-Meier estimate of time to virologic failure (consecutive viral loads above 400 copies/mL) stood at 10 percent 250 days after people started FTC. At 1,450 days that estimate had inched to 11 percent. The Kaplan-Meier probably of tolerability failure (permanent discontinuation because of death or toxicity) measured 13 percent after four years of FTC.

In a placebo-controlled comparison of FTC with d4T (plus didanosine [ddI] and efavirenz) involving 571 treatment-naive people, FTC outperformed d4T by every measure [abstract 606]. Resistance patterns in people who suffered virologic failure also painted an interesting picture. After 48 weeks of treatment, Pedro Cahn (Fundacion Huesped, Buenos Aires) reported, FTC won the primary endpoint battle—proportion with a viral load under 50 copies/mL—and several other contests (Table 4).

Among people who had a virologic failure, 71.4 percent taking FTC and 97.1 percent taking d4T had at least one resistance mutation ($P = 0.019$). In this virologic failure group, 42.9 percent taking FTC and none taking d4T had the M184V mutation ($P < 0.001$), 7.1 percent taking FTC and 20.0 percent taking d4T had a thymidine analog mutation (at positions 41, 67, 70, 210, 215, or 219) (not significant), none taking FTC and 11.4 percent taking d4T had the ddI-associated L74V mutation (not significant), 71.4 percent taking FTC and 88.6 percent taking d4T had an NNRTI mutation (not significant), and 28.6 percent taking FTC versus 2.9 percent taking d4T had wild-type virus ($P = 0.019$).

An open-label study randomized people with a viral load below 400 copies/mL while taking one or two PIs to continue the PIs or switch to a once-daily medley of FTC, ddI, and efavirenz [abstract 551]. Defining virologic failure as consecutive rebounds above 400 copies/mL, Jean-Michel Molina (Saint-Louis Hospital, Paris) found equivalent 48-week failure rates in the two groups by a missing-data-equal failure analysis: 22 of 177 (12 percent) for continued PI therapy and 18 of 178 (10 percent) for the once-daily FTC regimen. In an on-treatment analysis 95 percent taking once-daily therapy and 87 percent continuing PIs had a 48-week viral load below 50 copies/mL ($P = 0.01$). Kaplan-Meier estimates of serious side effects or treatment discontinuations disclosed no significant differences between groups.

Clinicians from Panama, South Africa, Mexico, and the United States studied FTC in 51 treatment-naive children and 31 experienced children, evenly divided between girls and boys and 72 percent of them black [abstract 872]. Ages ranged from three months to 17 years, and all took FTC at a dose of 6 mg/kg once daily to a maximum of 200 mg daily (the adult dose). Treatment-experienced children had viral loads below 400 copies/mL while taking a regimen including 3TC, which they replaced with FTC. Clinicians could also switch other drugs in the regimen.

In a week-24 noncompleter-equals-failure analysis, 63 percent in the naive group and 71 percent in the experienced group had a viral load under 50 copies/mL. Respective proportions below 400 copies/mL were 92 percent and 84 percent. Median follow-up extended to 31 weeks in the naive group and 48 weeks in the experienced group. Xavier Sáez-Llorens (Panama City) and colleagues attributed five severe toxic episodes to study drugs, including pancreatitis, vomiting, leukopenia, anemia, and pleural effusion. One treatment-naive child (2 percent) and four treatment-experienced children (13 percent) had a grade 3 or 4 lab abnormality. The researchers determined that the 6 mg/kg FTC dose yielded exposure similar to 200 mg once daily in adults.

And more, and more . . .

Atazanavir, GW433908, and tipranavir weren't the only new antiretrovirals—or even the only new protease inhibitors—to get PowerPoint treatment at the 10th CROI. Table 5 outlines 10 others, including two more PIs, a trio of nonnukes, a bevy of entry inhibitors, and a budding inhibitor. A few claims made for these hopefuls seem especially intriguing—or at least worthy of note:

- *TMC114*, Tibotec's PI, lowered viral loads 1.24 logs at a dose of 300 mg once daily, 1.13 logs at 900 mg once daily, and 1.5 logs at 600 mg twice daily in 38 people two weeks after they substituted TMC114 for a failing PI without changing other drugs in the regimen [abstract 8]. Most people had already tried three PIs. Although 73 percent of baseline viral isolates were sensitive to one or no PIs, their median fold change in susceptibility to TMC114 measured only 1.7.

- *RO033-4649*, Roche's third-millennium model PI, pitted against a panel of 50 "worst-case" viral isolates warehoused at ViroLogic, walked away with a mean IC_{50} of 100 nM, compared with 330 nM for amprenavir [abstract 7]. Roche found that 62 percent of these scurvy mutants evoked a 10-fold or lower change in susceptibility to RO033-4649.

- *Three benzophenone NNRTIs* from GlaxoSmithKline—tagged GW3011, GW4511, and GW4751—rank near efavirenz in *in vitro* activity against wild-type virus [abstract 6]. Unlike efavirenz, they score IC_{50}s below 10 nM against the notorious nonnuke mutations K103N, L100I, Y181C, and V108I, and against various double combinations of same.

- *TNX-355*, an anti-CD4 monoclonal antibody from Tanox requiring intravenous infusion, showed peak antiviral activity on the day when it completely coated CD4 cells in a short-term dose-ranging study [abstract 13]. TNX-355 lowered viral loads more than 1 log in five of six people getting 10 mg/kg and in five of six getting 25 mg/kg. The monoclonal antibody did not deplete CD4 cells. Researchers expect that regular dosing—most likely for people with limited oral-drug options—would be needed every one to three weeks.

- *Three CCR5 inhibitors* shared slide-session limelight—AK602 from Ono Pharmaceutical [abstract 10], TAK-220 from Takeda [abstract 11], and UK-427,857 from Pfizer [abstract 12]. Early studies of the latter two suggest they do not cause QTc interval prolongation, a heart rhythm worry that has dogged SCH-C, another entrant in this category. TAK-220 stifled HIV synergistically with ZDV, 3TC, indinavir, efavirenz, and enfuvirtide (T-20) [abstract 562]. All three of these CCR5 inhibitors could probably be oral agents.

Table 5. **What's so special about the new antiretrovirals?**

Drug (abstracts)	*Class*	*Developer*	*What's so special?*	*Study results*
GW433908 (fosamprenavir) (177, 178, 598)	PI	Glaxo	Amprenavir prodrug; only two 700-mg tabs daily when boosted with 100 mg of RTV; no food restrictions	In naive people, 55% <50 copies/mL at wk 48 vs 41% with NFV (177); in PI experienced, 1.5-log viral load ↓ with 908/RTV at 24 wk vs 1.66-log ↓ with LPV/RTV (178); in review at FDA
Atazanavir (555)	PI	Bristol-Myers Squibb	Once-daily dosing; modest effect on lipids; active against some PI-resistant virus	Viral load, total cholesterol, LDL-C, and TG ↓ after switch from 48 wk of NFV to ATZ; in review at FDA
Tipranavir (179)	PI	Boehringer Ingelheim	Active against some PI-resistant virus	No loss of susceptibility in people with virus harboring up to 3 key PI mutations; phase III trial began with 500/200 mg TPV/RTV twice daily
RO033-4649 (7)	PI	Roche	Active against some PI-resistant virus; more bioavailable than SQV; modest protein binding (~IDV)	Retained some activity against 31 of 50 "worst-case" viral isolates; in phase I
TMC114 (8)	PI	Tibotec	Active against some PI-resistant virus; once-daily dosing possible	Median 1.35-log viral load ↓ in 14-day study of 50 people with a median 3 PI mutations; in phase II
GW3011, GW4511, GW4751 (6)	NNRTI	Glaxo	Active against some NNRTI-resistant virus; modest effect of protein binding on activity	IC_{50} = 2 nM against wild-type HIV-1; IC_{50} from <3 to 17 nM against panel of wild-type and NNRTI-resistant viruses; one compound in phase I
FTC (emtricitabine) (550, 551, 606, 872)	NRTI	Gilead (formerly Triangle)	Once-daily dosing; superior to d4T in naive people at wk 48 of double-blind trial; may be combined in 1 pill with tenofovir	Durable viral suppression and good tolerability after switch from 3TC (550) or (with ddI and efavirenz) after switch from PI regimen (551); pediatric dose of 6 mg/kg once daily ~ adult 200 mg once daily (872)
T-1249 (14lb)	Fusion inhibitor	Trimeris/ Roche	Active against some T-20-resistant virus; once-daily sc dosing may be possible (instead of twice daily with T-20)	7 of 7 on failing T-20 for 24-48 wk had ≥1-log viral load ↓ with T-1249; 8 of 17 on failing T-20 for >48 wk had ≥1-log viral load ↓ with T-1249; in phase II
TNX-355 (13)	Anti-CD4 mAb	Tanox	Potent *in vitro* antiviral activity without immunosuppression; requires IV delivery	In dose-ranging trial in 30 people (19 on failing regimen), 1.5-log viral load ↓ with 10 mg and 1-log ↓ with 25 mg at day 14; no effect on $CD4^+$ cells; in phase I
AK602 (10)	CCR5 inhibitor	Ono	Higher binding affinity to CCR5 than SCH-C or TAK-779 (see next entry)	Active against spectrum of lab strains and primary R5-HIV isolates; once bound to CCR5-expressing cells, remains on cell surface >9 h and blocks HIV
TAK-220 (11)	CCR5 inhibitor	Takeda	Orally bioavailable (unlike forerunner TAK-779)	Active against 6 R5-HIV isolates in PBMCs at IC_{50} of 1.1 nM/L; 29% orally bioavailable in monkeys given 5 mg/kg; concentration in monkey lymph fluid 2 times concentration in plasma; no QTc prolongation in monkeys; phase I planned
UK-427,857 (12, 547)	CCR5 inhibitor	Pfizer	Active against isolates from multiple HIV-1 subtypes	Active against 43 lab strains and primary R5-HIV isolates from subtypes A-G, J, and O at IC_{90} <10 nM; no QTc prolongation in brief phase I trials; 100 mg twice daily achieves concentration >IC_{90}; absorption ↓ greatly with food
PA-457 (14)	Budding inhibitor	Panacos	Novel mechanism; orally bioavailable in rats with half-life of 2 to 3 hours	Active against NRTI-, NNRTI-, and PI-resistant virus; synergistic with ZDV, NVP, IDV

908 = GW433908; ATZ = atazanavir; IC_{50} = 50 percent inhibitory concentration; IC_{90} = 90 percent inhibitory concentration; IDV = indinavir; IV = intravenous; LDL-C = low-density lipoprotein cholesterol; LPV = lopinavir; mAb = monoclonal antibody; NFV = nelfinavir; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PBMCs = peripheral blood mononuclear cells; PI = protease inhibitor; RTV = ritonavir; sc = subcutaneous; SQV = saquinavir; TG = triglycerides; TPV = tipranavir.

- *T-1249*, the second-generation fusion inhibitor from Trimeris, has stirred interest even before its first-generation antecedent, T-20, hit the market. Unlike T-20, T-1249 may require only one subcutaneous shot daily, and it reined in viremia in people taking a failing regimen including T-20 [abstract 14lb]. Seven of seven people who had taken a faltering T-20 combo for 24 to 48 weeks had at least a 1-log viral load drop, while eight of 17 taking failing T-20 longer managed that feat. (Whether the hard-to-make and hard-to-take T drugs dovetail with daily practice will be interesting to chronicle. Most readers will have heard by now that a year's supply of the scant elixir T-20 will cost more than US$20,000—for the 12,000 to 15,000 expected to get the drug in 2003.)

Do people with HIV infection really need all these new antiretrovirals? That is probably not the apposite question, since only a handful of these candidates will survive the treacherous gauntlet that ends in the regulator's den. Some fast math shows that 18 percent of the antiretroviral philters in focus at the 1993 Retro gathering found spots on the pharmacy shelf, and one of those (delavirdine) pretty much stayed there. If a similar proportion of the 2003 meeting candidates wins a license, clinicians would have eight more antiretrovirals to add to today's 16.

With luck the next batch of anti-HIV meds will not merely inflate the current total, but will include agents of unique value. And—if the genie grants a second wish and a third—these drugs will be easy to take and will not require a home equity loan to pay for a year's dosing. Looking at the list of 45 debutantes on parade at the 10th CROI, and imagining the best of Panglossian worlds, one could envision:

- A once-daily PI that doesn't mess up lipids and fails with an unusual mutation
- Perhaps a few PIs and NNRTIs that frustrate resistant virus
- A small suite of entry inhibitors delivered with a glass of water instead of a needle
- A sprinkling of little pills that stymie viral integration, budding, or maturation

The amazing thing is that one can propose that list with a straight face.

OF COHORTS AND COPIES

Even as the promise of new, stronger, simpler, kinder antiretrovirals tantalizes, evidence suggests that the drugs at hand have flattened the epidemic—at least in Western Europe, North America, Brazil, and Australia. But whether lean hints of replication at sub-50 loads portend a load of trouble, or mere spillage, remains controversial.

"Excess deaths" now less excessive

The strongest sign that today's antiretrovirals can make HIV infection a chronic disease came from a EuroSIDA analysis of 3,793 people in the pre-HAART epoch (1994-1995), 3,425 in the early HAART era (1996-1997), and 2,585 in the late HAART age (1998-2002) [abstract 180]. The early HAART-propelled drop in new AIDS diagnoses and deaths has not bottomed out, Amanda Mocroft reported.

This incessant decrescendo reflects overall trends in CD4 counts of this cohort, which is now about three quarters male. Whereas people with 50 or fewer cells/mm^3 made up about 30 percent of the cohort in late 1994 and early 1995, they now account for fewer than 5 percent. The proportion with 51 to 200 cells/mm^3 ebbed from about 30 percent in 1994-1995 to about 15 percent today. Meanwhile, the group with more than 200 cells/mm^3 grew from 40 percent before HAART to over 80 percent today.

The risk of AIDS or death—adjusted for age, prior HAART, AIDS status, and CD4 count at cohort entry—fell from near 10 percent in 1994 and 1995, to 1 percent in late 1998 and early 1999, to less than 1 percent after September 2001. After September 1998, Mocroft figured the risk of AIDS or death slipped by 10 percent per six-month period ($P < 0.0001$). The incidence of death alone fell significantly during that period only among people whose latest CD4 count languished below 50 cells/mm^3. But the incidence of AIDS proved 50 percent lower in the late HAART era than in pre-HAART days regardless of CD4 count ($P < 0.0001$). In a multivariate model considering baseline differences, the risk of AIDS ($P = 0.0004$) or death ($P = 0.0013$) dropped by about one third from the early HAART era to the late HAART era.

Bernard Hirschel and Swiss HIV Cohort Study colleagues took a different tack in tracking the ongoing effect of HAART [abstract 917a]. They charted the "excess death rate" among HIV-infected people versus the population at large. Swiss HIV Cohort members still die at a faster rate than the whole population, but not faster than successfully treated cancer patients, "a group who is able to obtain life insurance."

In the EuroSIDA cohort the risk of AIDS or death slipped by 10 percent every six months after September 1998. In Switzerland the "excess death rate" with HIV (but without HCV) lies below that of successfully treated cancer patients.

The study involved more than 2,000 HIV-infected people (29 percent of them women) treated after January 1, 1997 and followed through the last day of 2001. People with HIV but without HCV had a substantially lower excess death rate than did those coinfected with HCV. Among people who reached a CD4 count above 250 cells/mm^3 with treatment, nadir CD4 count seemed not to affect mortality. Excess death rates range from 5 to 20 per 1,000 people per year among successfully treated cancer patients. Hirschel reported these excess death rates per 1,000 per year for HIV-infected people with or without HCV:

- Overall: HCV$^-$: 14, HCV$^+$: 38.1
- CD4 >250 cells/mm^3 on HAART: HCV$^-$: 4.2, HCV$^+$: 21.7
- CD4 >250 cells/mm^3 on HAART, RNA <400 copies/mL: HCV$^-$: 3.4, HCV$^+$: 20.5
- CD4 >250 cells/mm^3 on HAART, RNA >400 copies/mL: HCV$^-$: 8.0, HCV$^+$: 25.9
- CD4 >250 cells/mm^3 on HAART, CD4 nadir <250 cells/mm^3, RNA <400 copies/mL: HCV$^-$: 3.1, HCV$^+$: 23.3
- CD4 never above 250 cells/mm^3 on HAART: HCV$^-$: 117.4, HCV$^+$: 112.7

The Swiss team noted that keeping the viral load below 400 copies/mL appears to confer an extra survival benefit among people whose CD4 tally climbs above 250 cells/mm^3 with HAART.

Yet these macroviews of mortality may not reflect the microreality of individual clinics, reported W. Christopher Mathews from the Owen Clinic at the University of California, San Diego [abstract 911]. As elsewhere in Western Europe and North America, death rates began to plunge at that clinic in 1995, when better therapies for HIV and opportunists arrived. That trend continued downward until 1998—then turned back up. Analyzing data from nearly 5,000 people who entered the clinic from 1991 on, Mathews traced the post-1998 upswing to two groups—those who first sought care with a CD4 count below 200 cells/mm^3, and those with no CD4 data on file within 90 days of their first visit.

Looking more closely at 2,278 people who came to the clinic after 1997, Mathews noted nine factors that changed the risk of death stratified by year of entry:

- Hispanic heritage lowered the risk 0.66 times ($P = 0.036$)
- Injection drug use raised the risk 1.54 times ($P = 0.016$)
- Hospitalization before the first clinic visit raised the risk 2.07 times ($P < 0.0001$)
- An unknown antiretroviral history raised the risk 3.5 times ($P < 0.0001$)
- Entry CD4 count <50 (versus >350) cells/mm^3 raised the risk 13.8 times ($P <0.0001$)
- Entry CD4 count 50 to 199 (versus >350) cells/mm^3 raised the risk 4.8 times ($P <0.0001$)
- Missing CD4 count within 90 days of entry (versus >350 cells/mm^3) raised the risk 6.3 times ($P <0.0001$)
- Older age raised the risk 1.2 times per decade ($P = 0.037$)

Gender did not affect the risk of death in the post-1997 cohort. An entry CD4 count between 200 and 349 (versus more than 350) cells/mm^3 raised the risk 1.7 times, but that difference fell shy of statistical significance ($P = 0.089$).

Low-level viremia: smoke or fire?

Despite bringing the Western epidemic to a virtual standstill, today's antiretrovirals still suffer the steely-eyed scrutiny of scientists who can show that these drugs do not

stamp out every ember of replication. So the question becomes whether those smolderings yield only smoke, or also fire.

Jan van Lunzen (University Hospital Eppendorf, Hamburg) saw some ominous flickerings in lymphoid tissue of people taking apparently suppressive HAART [abstract 187]. All 32 study participants had viral loads below 25 copies/mL for more than nine months and had taken the same regimen for more than 12 months. Fourteen used a PI combination (only one with ritonavir boosting), 11 used a nonnucleoside, and seven used two or three nucleosides (including one taking two nucleosides and hard-gel saquinavir).

Axillary lymph node biopsies turned up productively infected cells in everyone, but the people taking only nucleosides had a much higher rate of viral trapping on follicular dendritic cells. Three of six in the nucleoside group, including one taking Combivir/abacavir and one taking two nukes plus hard-formula saquinavir, had HIV ensnared in dendritic tendrils. Only one of 14 taking a PI and none of eight taking an NNRTI had similar evidence. The M184V mutation arose during viremic blips in lymph nodes of the person taking Combivir/abacavir, but that mutation did not appear in peripheral blood mononuclear cells. Yet the nucleoside group didn't do much worse than the other groups when rated for HIV-infected germinal centers (16 of 26 samples overall) or HIV in extrafollicular tissue (21 of 26 overall).

Using a high-octane viral load assay with a dynamic range of 1 to 1,000,000 RNA copies/mL, Frank Maldarelli (National Cancer Institute [NCI], Frederick, Maryland) turned up viral traces in 14 of 15 people in whom a standard assay clocked viral loads below 50 copies/mL for at least 131 days [abstract 466]. In the 14 with these midgey loads, RNA numbers ranged from 1 to 40 copies/mL and averaged 9.3 copies/mL. Five people with serial measures had stubby but utterly stable loads for seven to 12 months. While higher pretreatment viral load correlated with higher low-level viremia, baseline CD4 count, treatment-induced CD4 change, and treatment duration did not.

Maldarelli also found that people taking four or more antiretrovirals had lower levels of Lilliputian viremia than did people taking only three drugs. "The apparent relation between regimen potency and level of viremia," the NCI team proposed, suggests sub-50-copy viremia "may be sustained by ongoing HIV-1 replication."

Does this runty replication portend full-fledged rebounds? Not according to results of a study of 12 children with viral loads below 50 copies/mL for one to six years [abstract 619]. Using an assay that spots 5 RNA copies/mL, Deborah Persaud and colleagues in Robert Siliciano's Johns Hopkins laboratory logged viral loads every three months in children who had kept an undetectable load since starting therapy or since switching to a PI regimen after taking suboptimal combinations. Persaud also managed to amplify and genotype viral samples from these children.

In 18 of 21 samples analyzed, the viral load always remained under 50 copies/mL. In three samples from three children, Persaud recorded blips to 69, 124, and 140 copies/mL. Sequencing 199 viral clones, she found that HIV spilling into plasma during suppressive HAART almost always proved wild-type or housed mutants that arose during earlier suboptimal therapy and hung on in the absence of drug pressure. There were two exceptions: The V82I protease mutation sullied two of six clones derived during a blip in a child taking nelfinavir. Another protease change, N88S, popped up in one of six clones from a nelfinavir-treated child with fewer than 20 copies/mL of circulating virus. Both children maintained viral suppression.

The Hopkins team concluded that "ongoing [low-level] viremia . . . during effective HAART in children represents release of largely archival drug-sensitive or drug-resistant HIV-1 rather than recently generated, drug-resistant mutations." Viremia below the 50-copy mark or blips below 200 copies/mL, they added, "does not necessarily represent impending therapeutic failure or the evolution of resistance and it therefore may not require a change in therapy." Earlier, Siliciano and colleagues failed to detect genotypic evidence of viral evolution in 11 adults with sub-50 viremia.[10]

Entr'acte

If compelled to posit a single conclusion from the last six studies—the cohort analyses by Mocroft, Hirschel, and Mathews, and the sub-50 fathomings of van Lunzen, Maldarelli, and Persaud—one might say this:

In people without a dire treatment history or untreated but dangerously advanced disease, improved regimens of recent years do a credible job of crippling HIV.

So why, as the 10th CROI amply demonstrated, do drugmeisters maintain their frenzied pace of discovery and development? This is an easy question to answer:

- Lots of people *do* have dire treatment histories.
- Lots have dangerously advanced disease.
- The others are living longer—and living laboratories of long-term side effects.

Those are the topics for Part 2 of this review, due next month. ■

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

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ABSTRACTS

Journal of Acquired Immune Deficiency Syndromes

Factors associated with the use of highly active antiretroviral therapy in patients newly entering care in an urban clinic

Giordano TP et al.

Ethnic minority, female, and drug-using patients may be less likely to receive highly active antiretroviral therapy (HAART), despite its proven benefits. We reviewed the medical records of a consecutive population of 354 patients entering care in 1998 at the Thomas Street Clinic, an academically affiliated, public, HIV-specialty clinic in Houston, to determine the factors associated with not receiving HAART as recorded in pharmacy records. Ninety-two patients (26 percent) did not receive HAART during at least six months of follow-up. Patients who did not receive HAART were more likely to be women and to have missed more than two physician appointments and were less likely to have a CD4 count <200 cells/μL or a viral load $\geq 10^5$ copies/mL. In multivariate logistic analysis, missed appointments (OR=5.85; $p < .0001$), female sex (OR=2.53; $p = .001$), and CD4 count ≥200 cells/μL (OR=2.50; $p = .001$) were independent predictors of not receiving HAART. More than half the patients who never received HAART never returned to the clinic after their first appointment. Among patients new to care, women and those with poor appointment adherence were less likely to receive HAART. Efforts to improve clinic retention and further study of the barriers to HAART use in women are needed.

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Journal of Medical Virology

Mutational patterns of paired blood and rectal biopsies in HIV-infected patients on HAART

Monno L et al.

Blood and concurrent rectal biopsy samples of human immunodeficiency virus type 1 (HIV-1)-positive highly active antiretroviral therapy (HAART)-treated patients were tested for genotypic resistance by direct sequencing of reverse transcriptase (RT) and protease (PR) regions to compare the patterns of resistance in these compartments. Fourteen subjects (five with undetectable plasma viral load (pVL) and nine persistently viremic) were studied. Four of five patients with undetectable pVL also had undetectable mucosal HIV RNA; sequence analyses from proviral DNA (PBMCs and rectal biopsy) were obtained with none or few resistance-associated mutations and no alteration of susceptibility profile. All viremic patients, and one with negative pVL, had detectable levels of mucosal HIV RNA (1.93 to 4.21 $\log_{10}$ copies/mg); sequences of HIV RNA (plasma and/or rectal biopsy) were also obtained, and multiple mutations generally compatible with current/past medications were detected. Overall, 40 HIV-1 PR and 42 RT sequences were analyzed, yielding a total of 42 PR and 47 RT sequence pairs (plasma/tissue-RNA; plasma-RNA/tissue-DNA; PBMC/tissue-DNA; tissue-DNA/RNA; tissue-RNA/PBMC-DNA; PBMC-DNA/plasma-RNA), which almost always differed at the total amino acid level (median percentage discordance 8.08 percent in the PR, 4.8 percent in RT). The median percentage of resistance position discordance equaled 88.8 percent (IQR = 20 to 100) in the PR and 74.55 percent (IQR = 31.75 to 100 percent) in the RT pairs, respectively. Different resistance levels were detected by means of a computer-assisted interpretation of mutational profiles. The results support the multiform evolution of HIV genotype in various body compartments and emphasize the participation of intestinal mucosa in HIV genotype selection. Samples from diverse tissues should be used for resistance evaluation to obtain a complete picture of drug resistance for antiretroviral-treated patients.

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Pediatric Infectious Disease Journal

48-week evaluation of lopinavir/ritonavir in HIV-infected children

Saez-Llorens X et al.

Lopinavir/ritonavir has demonstrated antiviral activity in the HIV-infected adult. The objective of this study was to investigate a liquid coformulation of lopinavir/ritonavir, in combination with reverse transcriptase inhibitors, in HIV-infected children. One hundred antiretroviral (ARV)-naive and ARV-experienced, nonnucleoside reverse transcriptase inhibitor-naive children between six months and 12 years of age participated in this Phase I/II, open label, multicenter trial. Subjects initially received either 230/57.5 mg/m or 300/75 mg/m lopinavir/ritonavir twice daily; ARV-naive subjects also received stavudine and lamivudine, whereas ARV-experienced subjects also received nevirapine and one or two nucleoside reverse transcriptase inhibitors. Lopinavir/ritonavir pharmacokinetics, safety and efficacy were evaluated. All subjects were escalated to the 300/75 mg/m twice daily dose based on results from an interim pharmacokinetic and safety evaluation. The pharmacokinetics of lopinavir did not appear to be dependent on age when dosing was based on body surface area but were decreased on coadministration with nevirapine. Overall 79 percent of subjects had HIV RNA levels <400 copies/ml at Week 48 (intent-to-treat: missing = failure). Mean increases in absolute and relative (percent) CD4 counts from baseline to Week 48 were observed in both ARV-naive subjects (404 cells/mm; 10.3 percent) and ARV-experienced subjects (284 cells/mm; 5.9 percent). Only one subject prematurely discontinued the study because of a study drug-related adverse event. The researchers concluded that the liquid coformulation of lopinavir/ritonavir demonstrated durable antiviral activity and was safe and well tolerated after 48 weeks of treatment in HIV-infected children.

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Mount Sinai Journal of Medicine

Hypersensitivity reactions to drugs: Evaluation and management

Shepherd GM.

Most hypersensitivity reactions to drugs occur within several weeks of administration; signs and symptoms are often consistent with known immune-mediated reactions, including anaphylaxis, rashes, fever, cytopenias and vasculitis. The culprit immune mechanisms range from immunoglobulin E antibody to T cells inducing apoptosis of keratinocytes, in the case of bullous exfoliative rashes. Many drugs induce reactions via altered hepatic metabolism, with production of reactive intermediates that induce a common syndrome of rash and fever plus variable types of other signs. Examples of this reactive metabolite syndrome include the rash and fever in HIV-positive patients given sulfamethoxazole and reactions to the aromatic anticonvulsants. With the notable exception of anaphylaxis and severe bullous exfoliative rashes, most immune reactions to drugs are not life threatening and generally resolve once the drug is discontinued. The key is prevention. Specific immune testing is standardized only for penicillin. If test results are negative, however, the patient can tolerate all beta-lactam antibiotics. Of those patients with a positive penicillin skin test, only 2 percent develop reactions when given cephalosporins. Sulfa and quinolone antibiotics, and muscle relaxants, also frequently induce reactions. If there is a history of bullous rash, the patient should never again receive sulfa or quinolone, or related drugs. In other cases, a cautious graded challenge or desensitization can be done. Vancomycin, protamine, and radiocontrast media induce non-immune reactions secondary to their irritant effects on vascular endothelium. Narcotic pain medications cause histamine release by binding to a specific receptor on mast cells in sensitive patients. In contrast to true immune reactions, most patients can receive these medications again, if they are pretreated and the drugs are given slowly. Angiotensin-converting enzymes, aspirin, and non-steroidal anti-inflammatory drugs induce adverse reactions by their effect on enzymes. Readministration usually results in repeat symptoms. It is possible to desensitize patients to aspirin. Some patients appear to develop similar adverse symptoms with multiple unrelated drugs. Although these cases present management problems, most patients can complete a therapeutic course of a vital drug, after careful review of the history, immune testing when possible, and graded challenge or desensitization.

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IN THE LIFE

Corklin Steinhart

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 Corklin Steinhart, who is Medical Director for the Florida Caribbean AIDS Education Training Center and Senior Attending Physician at Mercy Hospital in Miami.

What proverb, colloquial expression, or quote best describes how you view the world and yourself in it?
"Our doubts are traitors and make us lose the good we oft might gain by fearing to attempt."

What activities, avocations, or hobbies interest you?
Travel, yard work, and reading.

If you could live anywhere in the world, where would it be?
The good old US of A! Not perfect, but better than anywhere else!

Who are your mentors or real life heroes?
Mentors: My father, his father, graduate school advisor. Real Life Heroes: Those people who have risen above the meager circumstances to which they were born.

With what historical figure do you most identify?
None — Sorry!

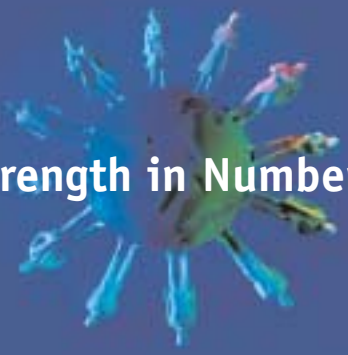
Who are your favorite authors, painters, and/or composers?
Authors: Eugene O'Neill, Chaim Potok. Painters: Rembrandt, any of the 19th century impressionists. Composers: Mozart, Prokofiev, Paul McCartney.

If you could have chosen to live during any time period in human history, which would it be?
The present! Because of its dynamic nature and our ability to do most everything we want if we set our collective minds to it!

If you did not have the option of becoming a physician, what would you have likely become given the opportunity?
An exercise physiologist or an archeologist. Oh, yes, an astronaut, too.

In your opinion, what are the greatest achievements and failures of humanity?
Greatest achievements: The wheel, automobile, TV, computers, democracy. Greatest failures: Organized religion, inability to accept differences in other peoples.

What is your prediction as to the future of our planet one full decade from present day?
I am fearful of where we are heading unless we can accept the differences we have and realize that we must all work together for the betterment of us all. If we can get through the next decade, the sky is the limit! ■



[Strength in Numbers]

[IAPAC Welcomes New and Renewing Members]

The International Association of Physicians in AIDS Care (IAPAC) welcomed 35 new and renewing dues-paying members in March 2003. 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.

Nancy Angoff, *USA*
Joseph Arino, *USA*
Roberto Aymat, *USA*
Susan Balter, *USA*
Joseph Caperna, *USA*
Alexander Chun, *USA*
Paul Cimoch, *USA*
Rod Felber, *USA*
Lisa Gooze, *USA*
Kathryn Hall, *USA*
David Hart, *USA*
Madelene Heck, *USA*
Taesoo Kim, *USA*
Lisa Kohler, *USA*
Patricia Langehennig, *USA*
Joanne Levin, *USA*
John McCarthy, *USA*
J. Allen McCutchan, *USA*
John Mellors, *USA*
Richard Morin, *USA*
Alawode Oladele, *USA*
Jeffrey Olliffe, *USA*
Paul Palumbo, *USA*
Cathryn Samples, *USA*
James Sampson, *USA*
Richard Saulle, *USA*
Mark Scheperle, *USA*
Mary Singer, *USA*
Lorraine Tosiello, *USA*
Lisa Veach, *USA*
Ronald Wing, *USA*

Also in March 2003, the following institutions joined IAPAC as institutional members: Clinical Directors Network; Other Options, Inc.; and Philadelphia Department of Public Health.

For more information regarding professional and institutional memberships, call (312) 795-4935 or send an e-mail to member@iapac.org. To learn about 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 2002, 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.

Testing for competence...

Continued from page 73

regions, is convened with these goals in mind. (A full list of GALEN Certification Committee members is available on IAPAC's Web site: www.iapac.org.)

What should the test look like?

There are several components as follows:

- *Blueprint:* The blueprint defines the content by category of information being tested. For example, there may be 10 percent of questions allocated to antiretroviral therapy, 10 percent for prophylaxis and management of opportunistic infections, etc. Physicians knowledgeable in clinical care of HIV, especially as it is practiced in resource-limited settings, defined the blueprint for the GALEN certification examination as articulated in Table 1.
- *Question format:* The time-honored examination format, based on psychometrics, is to use "type A questions," which have a stem and five options, only one of which is correct. The GALEN certification examination uses this format.
- *Question characteristics:* Most of the examination is composed of "questions of knowledge" and "questions of judgment." An example of a knowledge question is: "Which of the following is the most common side effect of nelfinavir?" A question of judgment is: "Which of the following is the most important test in a patient with fever, headache, ALC of 460 cells/mm^3 and HIV infection?" There should also be some questions dealing with ethics, but it should be emphasized that this needs to be a small portion of the examination, not because ethics are unimportant, but because ethics is best documented by behavior rather than by performance on an examination.
- *Question phrasing:* This is not an examination of examination taking, but an examination of medical competence. All questions must be clinically relevant; all the necessary information that would be readily available at the bedside should be provided, and the examination should carefully avoid ambiguities. Double negatives should be avoided, for example: "Which of the following is not uncommon" would be a poor way to phrase an examination question. Terms such as "common," "rare," and "frequent," should be avoided because it is unclear, for example, if "uncommon" means less than 50 percent, less than 10 percent, or less than 1 percent.
- *Consensus:* The GALEN Certification Committee must agree on each answer, and each answer must be indisputably correct. The challenge here is great because there are so many clinically important questions whose answers are either arbitrary or subject to rapid change.

How do we know if it's a good test?

The following are generally accepted measures that will be employed by the GALEN Certification Committee:

- There should be a "practice run" of persons with established expertise who take the examination to determine if it is fair.
- There needs to be agreement that the questions are relevant to clinical practice. It is nice to know the replication rate of HIV, and how HIV enters the CD4 cell, but this information is not important for clinical care and it is, therefore, unfair to ask about it on the examination.
- There needs to be a determination of the "pass score." There are two methods to do this: First, there may be an arbitrary passing grade such as 75 percent of all who take the examination. An alternative method is the "Angoff" method in which a group of experts decide the number of people with reasonable medical competency that would get each question correct; this is then used to determine the pass score. There may be some questions that are weighted simply because of their relative importance. At its next meeting, the GALEN Certification Committee will determine a method for setting the GALEN certification examination's "pass score."

Question analysis: The perfect question will be answered correctly by about 75 percent of those writing the examination. Incorrect responses should be distributed relatively evenly among the four other choices. Having a question that 95 percent of participants answer correctly does not help the examination; likewise, a question that almost all participants miss should be avoided.

An additional method of analysis is to review the performance of the top 20 percent of examination takers for each question with the assumption that the "smart group" will do especially well on a "good" (read: well-constructed) question.

Post-hoc analysis: The GALEN certification examination will be evaluated using the methods above. Questions will be discarded if they are viewed, in retrospect, as too hard, or too easy. Questions would also be eliminated if the correct answer has changed, or new information has made that answer debatable. Sometimes a question simply does not perform well. In many such examinations, up to one half of the entire examination is discarded by this post-hoc analysis. Many questions are preserved because they do extremely well and can be used in subsequent years. One benefit of this tactic is to compare performance from year to year to know if the examination takers are getting better. Re-using questions, of course, requires that the test is secure—that the people sitting the examination cannot leave the examination area with a copy of the examination, for example.

Updating: The GALEN certification examination will be updated on a frequent basis; at least annually. This is to reflect new developments in the field, which are especially relevant to the topic of HIV clinical management, in which new developments occur often. Frequent updating will require the GALEN Certification Committee to communicate regularly and work hard.

Credentialing: It is emphasized that examination results are only one component of the credentialing process. Other facets of the credentialing process may include a training requirement, medical licensure, clinical experience, and documentation of professionalism. In the case of GALEN certification, we have determined that only physicians with a locally valid medical license and documented experience treating HIV-infected patients may sit the examination. The examination is just one component of the credentialing process, but a very important one. The hope and anticipation is that a good examination, created by appropriate experts in the field, will stand as testimony of medical competence and serve as the most important component of the GALEN certification process. ■

John G. Bartlett is Chief of Infectious Diseases at the Johns Hopkins University School of Medicine in Baltimore, and Co-Chair of the GALEN Certification Committee.

SAY ANYTHING

People with HIV are living longer, no question about it, and that is something we're very pleased about. However, much remains unclear. What is the long-term efficacy of anti-AIDS drugs, for example? Also, since new HIV infections continue to occur, we must remain focused on HIV prevention and keep positive trends in perspective.

Julie Gerberding, Director of the US Centers for Disease Control and Prevention (CDC), quoted in a March 15, 2003, New York Times *article. The CDC partially attributed a rise in average US lifespan to the fact that patients living with HIV/AIDS, most of whom are on antiretroviral therapy, live years longer than they did before the development of such therapy.*

What we are saying is that unless the governments take part and there is guaranteed predictability [of demand], there is no incentive to produce and supply these drugs. If I am giving it at a humanitarian price, then we should have guaranteed predictability, and payment.

Y.K. Hamied, Chairman of the Indian pharmaceutical firm Cipla, in explaining to a reporter why his company may stop producing generic versions of antiretroviral drugs. A March 18, 2003, Reuters report discussed how patent restrictions and a lack of funding even for much cheaper generic HIV-treating medications have moved Cipla and other Indian pharmaceutical companies to reconsider their continued manufacture of these drugs. Cipla began selling a complete antiretroviral regimen in February 2001 at the greatly reduced price of less than US$1 per day. However, in many countries of southern Africa, where HIV/AIDS is most prevalent, annual medical spending is less than US$2 per person.

There is substantial dissonance between much of the epidemiologic evidence and the current orthodoxy that nearly all of the HIV burden in sub-Saharan Africa can be accounted for by heterosexual transmission and the sexual behavior of Africans.

Devon D. Brewer et al. in the March 2003 issue of the International Journal of STD & AIDS. *In reviewing existing research evidence, three papers in the issue asserted that unsafe medical practices are a likelier explanation than unsafe sex for the world-leading HIV incidence rates in southern Africa. The assertion, which disputes a consensus among public health experts that has held since 1988, sparked immediate controversy. The World Health Organization (WHO) issued a March 27, 2003, statement, drawing on the opinions of "an expert group," declaring "unsafe sexual practices are responsible for the vast majority of HIV infections in sub-Saharan Africa, and that safer sex promotion must remain the primary feature of prevention programs in the region." The statement went on to say that unsafe injections should nonetheless be addressed, citing a figure that as many as 30 percent of the world's 16 billion annual medical injections are performed with unhygienic syringes.*

Photo: C WHO/P. Virot

By redoubling our efforts—and with strengthened funding for the Global Plan to Stop TB—we could expect to see a reduction in the sickness and death caused by tuberculosis worldwide within the next few years, as we are already seeing in some countries like Peru. But we stand at a crossroads in this struggle and must not lose our direction and momentum. If we falter in our efforts at this crucial juncture, the hard-won progress of the past decade could easily be halted and even reversed.

Jong Wook Lee, Director-General nominee of the World Health Organization (WHO), speaking at a March 24, 2003, World TB Day press conference in London during which he explained that for the first time since the WHO declared tuberculosis a "global emergency" in 1993, there are real prospects for turning the tide against the epidemic. Lee said the accumulating number of patients cured under DOTS, the internationally recommended tuberculosis strategy, has clearly slowed the spread of infection and signals a significant public health development. According to the WHO, the number of countries that have adopted the DOTS strategy has grown from fewer than 20 in 1993 to 155 in 2003. Indeed, more than 60 percent of the world's population now have access to free DOTS services, according to the WHO's "2003 Global TB Control Report."