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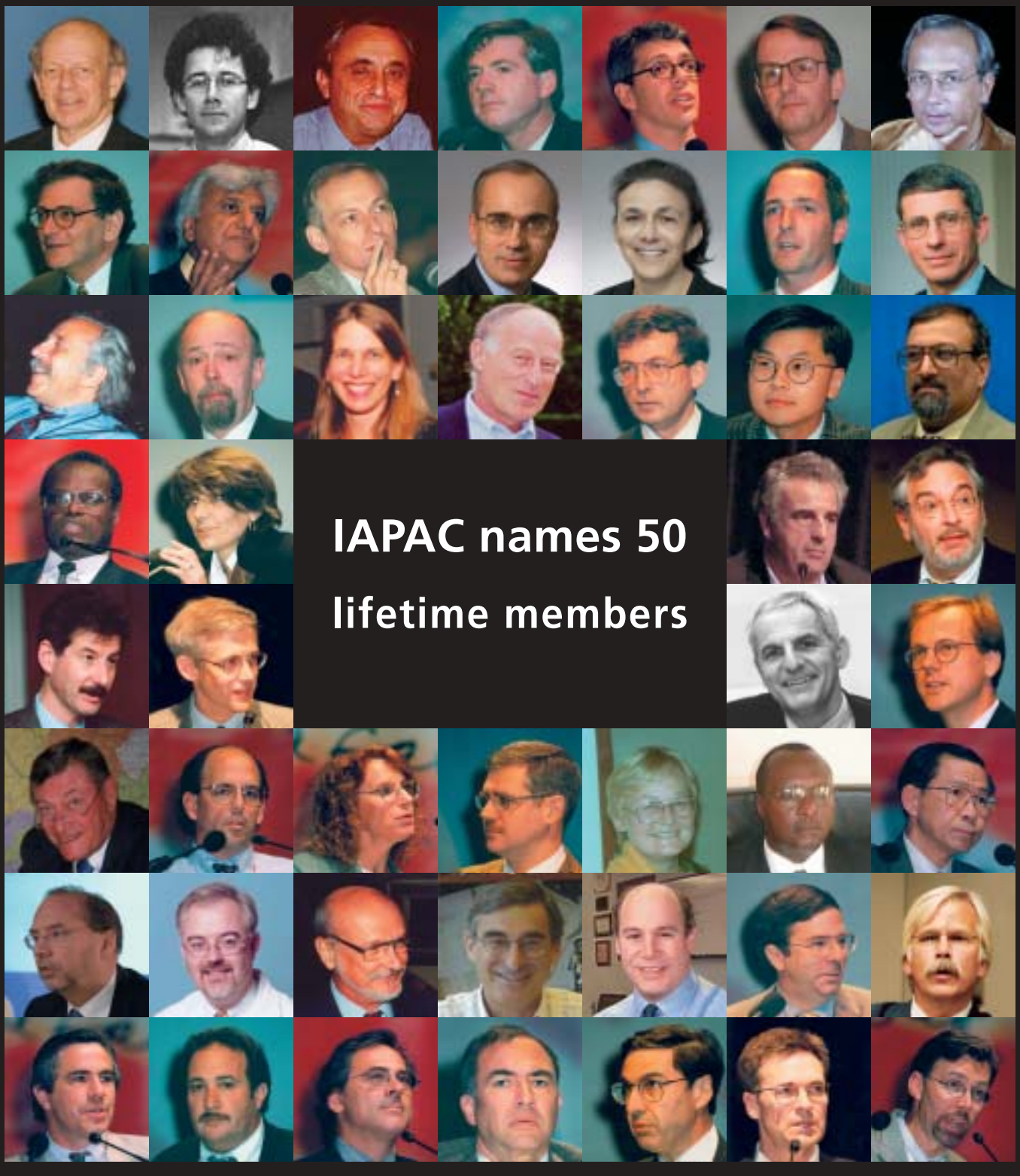
IAPAC

MONTHLY



IAPAC names 50 lifetime members

September 2005

IAPAC MONTHLY

Volume 11, Number 9

256

IAPAC names 50 lifetime members

5 × 10

José M. Zuniga

In commemoration of the 10th anniversary of the International Association of Physicians in AIDS Care (IAPAC), 50 men and women have been conferred honorary lifetime membership in the 12,800 member-strong association. Their faces grace this month's cover, and their names are contained in IAPAC President/CEO José M. Zuniga's monthly report.

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IAPAC

battling complacency
advancing commitment

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

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

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

EXECUTIVE DIRECTOR Nathalie C. Kaunda
DEPUTY DIRECTOR Jaz Hughes

IAPAC MONTHLY

EDITOR-IN-CHIEF José M. Zuniga
MANAGING EDITOR Lisa McKamy
CREATIVE/DESIGN DIRECTOR Holly J. Emanuelson
ADVERTISING DIRECTOR Cathy Córdova
WRITER-AT-LARGE Mark Mascolini
CONTRIBUTING WRITERS
Michael Carter, Carrie Scharrer

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REPORT FROM THE PRESIDENT

5×10

José M. Zuniga

The cover of this month's *IAPAC Monthly* reflects a tapestry of dedicated individuals from around the world who are at the vanguard of HIV/AIDS care and research. They are by no means an exclusive group, for standing shoulder to shoulder with them in the global battle against HIV/AIDS, either literally or figuratively, are hundreds of thousands of their peers. On the occasion of the 10-year anniversary of the creation of the International Association of Physicians in AIDS Care (IAPAC), these 50 individuals (five for each year since IAPAC's incorporation) are being conferred honorary lifetime membership in our 12,800 member-strong association. Five more will join their ranks each year that IAPAC continues to exist and deliver services worldwide.

The 50 individuals listed in the sidebar article accompanying this Report from the President and pictured on the cover have in one way or another shaped our fight against HIV/AIDS. They were nominated by a select group of their peers as well as patient advocates who work with IAPAC to advance medical and patient education and support initiatives, respectively.

It is always difficult to narrow a field of candidates, especially when there are so many gifted and dedicated physicians at the frontlines of HIV/AIDS care and support. And, frankly, it is difficult at times to ensure that such exercises do not become popularity contests. To those physicians who are not on this year's list, know that IAPAC values your expertise and commitment. To those who look upon the cover and chalk the exercise up to a popularity contest, rest assured that the only criteria used in selecting these members were their dedication and unflagging efforts and the respect and recommendation of their peers. As new honorary lifetime members are inducted into our ranks, we would like this list to become even more diverse, with representatives from around the world and from the realms of research as well as clinical practice.

It has been a pleasure and an honor to work with so many leaders in HIV research, medicine, and education, and it is an even greater honor to recognize a few of these individuals as we commemorate our association's 10th anniversary. Our members are the key to IAPAC's continued vitality and growth, and though we can only honor 50 today, we hope to convey through this gesture the importance of all our members to the future of IAPAC and the work we advance throughout the world. ■

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

Honorary IAPAC lifetime members

Fifty men and women from 17 countries were conferred honorary lifetime membership in the International Association of Physicians in AIDS Care (IAPAC) in September 2005.

1. John G. Bartlett, *United States*
2. Charles Boucher, *Netherlands*
3. Pedro Cahn, *Argentina*
4. Bill Cameron, *Canada*
5. Andrew Carr, *Australia*
6. Richard Chaisson, *United States*
7. Bonaventura Clotet, *Spain*
8. David Cooper, *Australia*
9. Hoosen Coovadia, *South Africa*
10. Kevin DeCock, *United States*
11. Douglas T. Dieterich, *United States*
12. Wafaa El-Sadr, *United States*
13. Joseph J. Eron Jr., *United States*
14. Anthony Fauci, *United States*
15. Gerald Friedland, *United States*
16. Brian Gazzard, *England*
17. Diane V. Havlir, *United States*
18. Martin S. Hirsch, *United States*
19. Bernard Hirschel, *Switzerland*
20. David D. Ho, *United States*
21. Salim A. Karim, *South Africa*
22. Elly Katabira, *Uganda*
23. Christine Katlama, *France*
24. Michel Kazatchkine, *France*
25. Donald Kotler, *United States*
26. Daniel R. Kuritzkes, *United States*
27. Clifford Lane, *United States*
28. Joep MA Lange, *Netherlands*
29. Jens Lundgren, *Denmark*
30. Des Martin, *South Africa*
31. John W. Mellors, *United States*
32. Lynne Mofenson, *United States*
33. Julio S.G. Montaner, *Canada*
34. Veronica A. Moss, *England*
35. Peter Mugyenyi, *Uganda*
36. Praphan Phanuphak, *Thailand*
37. Peter Piot, *Switzerland*
38. William G. Powderly, *Ireland*
39. Celso Ramos-Filho, *Brazil*
40. Douglas Richman, *United States*
41. Michael S. Saag, *United States*
42. Robert T. Schooley, *United States*
43. Renslow Sherer, *United States*
44. Robert F. Siliciano, *United States*
45. Schlomo Staszewski, *Germany*
46. Stefano Vella, *Italy*
47. Paul A. Volberding, *United States*
48. Mark Wainberg, *Canada*
49. Bruce D. Walker, *United States*
50. Andrew R. Zolopa, *United States*

Editor's Note: Shown on the cover in alphabetical order, left to right, top to bottom row.

2002 TOP 10

10 Most Important Developments in HIV Medicine

1. Two new antiretroviral drugs became available in expanded access programs: enfuvirtide, the first fusion inhibitor, and atazanavir, a new protease inhibitor.
2. Ukraine became the first European nation with an HIV infection rate of 1% of its adult population.
3. US Secretary of State Colin Powell distanced himself from the views of the Bush Administration by strongly advocating condom use to prevent the spread of HIV and other sexually transmitted diseases.
4. Richard Feachem was selected as the first Executive Director of the Global Fund to Fight AIDS, Tuberculosis and Malaria. In the first round of applications, more than six times the number of requests anticipated were received. The Global Fund announced its first round of payments, a total of US$600 million over a two-year period. In December 2002, the first disbursement of US$1 million was made.

5. The World Health Organization (WHO) released "Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Guidelines for a Public Health Approach," which included guidelines for providing antiretroviral therapy to HIV-infected people in developing countries. At the WHO's 12th Expert Committee on the Selection and Use of Essential Medicines Meeting, the committee added 12 antiretroviral drugs to its Model List of Essential Medicines.
6. GlaxoSmithKline submitted data to the US Food and Drug Administration (FDA) supporting the approval of fosamprenavir, a prodrug of the protease inhibitor amprenavir, with improved bioavailability and a reduced pill burden.
7. The number of children orphaned by AIDS reached an estimated 13.4 million.
8. Swiss researchers reported the first documented case of "superinfection," in which an HIV-positive man was infected with a second strain of HIV through unprotected sex more than two years after he was first infected.

9. The South African version of *Sesame Street*, called *Takalani Sesame*, added Kami, an HIV-positive character, whose name is taken from a Tswana word for "acceptance."
10. A United Nations (UN) report stated that for the first time women made up half of all adult cases of HIV worldwide.

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XIV INTERNATIONAL HIV DRUG RESISTANCE WORKSHOP

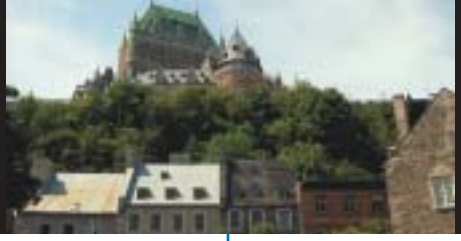
JUNE 7-11, 2005
QUÉBEC, CANADA

The squirming facts exceed
the squamous mind,
If one may say so...

—Connoisseur of Chaos,
Wallace Stevens

Are resistance puzzlers caught in a data quagmire?

Mark Mascolini



Sorting winners from losers has never been easy in Québec, starting with the storied battle on the Plains of Abraham. Canadian schoolchildren can recite the details of that 1759 tussle:

British general James Wolfe sweet-talked 385 soldiers into scaling the 53-meter precipice that soars from the St. Lawrence River to the Plains of Abraham. Heading the French forces, General Louis-Joseph de Montcalm left only 100 defenders at the cliff's verge, certain that Wolfe would never essay such a daring dodge.[1] But the Brits got a foothold on the Plains, sent another 5,000 troops shinnying up behind, and routed the French.

The fracas marked the end of French dominion in North America. Yet who really won remains hard to say. Montcalm succumbed to grievous wounds, as did Wolfe. In the Treaty of Paris, France traded the sere continental wastes of "New France" for the lush but tiny Guadaloupe. The British queen's head now graces Canada's coins. But for some reason they still speak French on the streets of Québec.

English was the official language of the XIV International HIV Drug Resistance Workshop, but the site was the Château Frontenac on rue des Carrieres in Québec Ville. And the workshop pivot proved familiar—sorting winners from losers in puzzling out resistance to antivirals.

The 21-item mutation set for tipranavir may seem excessive to some. But with eight other protease inhibitors already on the market and a world of cross-resistant virus at large, a 21-item list could end up seeming mercifully brief.

One would think—after scaling the slick cliffs of resistance for 15 years—High Science would have a purchase on the grassy Plains of Sapience. We have had genotyping and phenotyping (vanilla and virtual), fuzzy logic and flexible semiparametrics, inhibitory quotients (plain, genotypic, virtual, and normalized), neural networks, machine learning, causal inference, and case-based learning. We have had algorithms *ad hoc*, *ad lib*, *ad rem*, and *ad unguem*. We have had controlled trials.

But what have they taught about reckoning resistance? What do they tell about planning the next regimen?

If a writer groping for some sizzle to start yet another resistance article posed these questions, one might read on insouciantly. But these questions came from the very clerisy of resistance research—deep thinkers like John Mellors (University of Pittsburgh), keen clinicians like Andrew Zolopa (Stanford University).

After sitting through 10 minutes of Zolopa's studied review of resistance scores and cutoff decoctions, the rarely reticent Mellors rose. At best, he proposed, these teeming tries to interpret resistance have yielded only incremental progress—for those brave enough to breast the consequent "quagmire of data."

Zolopa, whose pithy gloss on expert resistance analysis bared both its muscle and its dystrophy,[2] went further. Accreting interpretive systems have not edged knowledge forward, he feared. They have made him more confused.

This is a scary confession from one of the field's brightest guys—someone you might call to shepherd you through a brambly genotype. Zolopa's lament suggests less that he is losing ground than that less savvy medics underrate the odds they face.

One can cipher those odds' length from many a recent proposal. Take, for example, Boehringer Ingelheim's advice that clinicians thumb a list of 21 mutations at 16 protease positions when sizing up potential resistance to tipranavir (TPV) (see abstract 27).[3] Some scoff at the suggestion. But with eight other protease inhibitors (PIs) already on the market—and a world of cross-resistant genotypes at large—a 21-item list may end up seeming mercifully brief.

Attempts to hew clean paths through genotypic thickets leave many unimpressed. Brendan Larder (HIV Resistance Response Database Initiative, Cambridge, UK), who with others *discovered* thymidine analog mutations (TAMs), scoffed at simplifying maps of TAM-1 and TAM-2 paths. Deenan Pillay (Health Protection Agency, London), owner of a most penetrating mind, judged such paths not simplifying but simplistic.

Workshop attempts to divine the clinical import of resistance to boosted PIs—or to familiar nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)—impressed with their cunning but left attendees wondering about their worth.

Then there's the K65R saga—now approaching Homeric proportions even though most research suggests it doesn't really arise much.

Of course this 14th edition of the fabled Resistance Workshop did more than sow doubt, brew discord, or divine dead ends. Two hundred attendees learned that:

- Yes, crystal methamphetamine does inspire high-wire sex stunts by people with resistant virus [abstract 117]; though,
- No, dual-tropic, triple-class-resistant virus does not get transmitted much [abstract 128]; but,
- Yes, people infected with resistant virus risk a subpar response [abstract 114]; and,
- Indeed, transmitted mutations stuck in semen revert slowly [abstract 115].
- While Combivir does trim the risk of resistance after single-dose nevirapine (NVP) [abstract 2],
- It does not eliminate that risk [abstract 3].
- And although multidrug resistance fosters nearly 10% mortality in two years [abstract 5],
- Even a single mutation may pave a faster track to disease progression [abstract 32].

INTO THE WOODS WITH ATAZANAVIR/RITONAVIR

The flurry of reports that so vexed workshop worthies about the interpretive merits of resistance data all came in the first day's second slide session, "Prediction of Clinical Response." Three groups proffered schemes to predict response to atazanavir/ritonavir (ATV/RTV) and one wrestled with multiple methods to forecast results to abacavir (ABC) and didanosine (ddI). Others essayed the clinical virtue of defining TAM-1 and TAM-2 pathways.

Tradeoffs on cutoffs for ATV/RTV

ViroLogic's phenotyping assay sets a 2.3-fold cutoff for response to ATV. But with RTV boosting now virtually a *sine qua non* of ATV therapy, is 2.3 precise? To find out, Eoin Coakley and ViroLogic colleagues sifted findings from two trials of this once-daily PI—BMS AI424-043 (which randomized people with a PI failure to unboosted ATV or lopinavir (LPV)/RTV) and BMS AI424-045 (which randomized people in whom two regimens floundered to ATV/RTV or LPV/RTV) [abstract 6].

Three tries to interpret genotypic talismans in ATV trials—and separate attempts to reckon the merits of ABC and ddI algorithms—inspired more head scratching than seen in the average shampoo commercial.

Everyone in this analysis stuck with their assigned regimen for 24 weeks. Coakley defined the clinical cutoff as the lowest fold-change in viral susceptibility to ATV above and below which he discerned statistically distinguishable differences in viral control rates.

The 043 trial cross-exam involved 131 people who started unboosted ATV at a mean ATV fold change of 2.9. These people had tried PIs for a median 2.6 years, but only 36% were taking a PI when they began unboosted ATV. About one third had four or more major protease mutations. At the 24-week mark, 83 (66%) had a viral load under 400 copies/mL.

Using Fisher's exact test to fish for clinically relevant ATV cutoffs in the 1.6- to 5.1-fold range, Coakley settled on 2.2 as the sharpest cut point. Among people with a baseline fold change below 2.2, 76% had a sub-400 load at week 24. Among those whose baseline fold change measured 2.2 or more, 45% met the week-24 response criterion.

The 045 trial inquest probed for cutoffs in 111 people who started ATV/RTV with an average ATV fold change of 4.1. This group had tried a median of two regimens and logged 2.6 years of PI experience. Yet they had only a median of two main PI mutations, and only 44% had three or more mutations from the Stanford database of 16 ATV- or LPV-linked mutations.

Taking the same statistical approach as in the 043 analysis, Coakley homed in on a cutoff of 5.2. Among people whose susceptibility to ATV lay below 5.2 on enrollment, 77% had a viral load below 400 copies/mL at week 24, compared with 12% with a baseline cutoff of 5.2 or more.

Coakley prudently cited three caveats to this analysis:

- The models did not account for the impact of other drugs in the ATV regimens.
- People in the 045 trial took tenofovir (TDF) with ATV and so probably attained lower concentrations of the PI.
- Only 34% of 045 study participants were taking a PI when enrolled.

Combined, these factors may have lowered the clinical cutoff for ATV/RTV, and somewhat less for ATV alone. So the 2.2- and 5.2-fold thresholds can be considered conservative estimates.

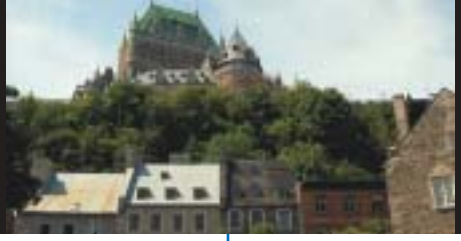
With Swiss and French coworkers, Anne-Genevieve Marcelin (Geneva University Hospital) took a different path to truffle for ATV response predictors in PI-experienced people—a genotypic resistance score [abstract 7]. Her heuristic began with 62 people who switched to ATV/RTV with a viral load above 1,000 copies/mL because of virologic failure (84%) or intolerance (16%).

The group had tried a median of two PIs and had a median baseline load of 4.3 log copies/mL (about 20,000 copies/mL). A hefty proportion—69%—took TDF with ATV/RTV. After three months on their new regimen, 82% had at least a 1-log (10-fold) drop in viral load.

Testing mutations with a prevalence above 8%, Marcelin gleaned 25 substitutions at 13 positions that dented response to ATV/RTV: 10F/I/V, 16E, 33I/F/V, 46I/L, 54L/V/M/T, 60E, 62V, 71I/T/V/L, 82A/T, 84V, 85V, 90M, and 93L. The strongest statistical tie to poor response involved mutations at seven sites—10F/I/V, 16E, 33I/F/V, 46I/L, 60E, 84V, and 85V ($P = 8.04 \times 10^{-9}$, which means 804 lies eight zeros away from the decimal point). Notably, no genotypic roadmap to ATV resistance lists mutation milestones at positions 16, 60, and 85. The 14 mutations in the resistance score authored by Bristol-Myers Squibb did not predict this response better than Marcelin's septet.

One-log response rates tailed off sharply in people who piled up two, three, or more of these seven treacherous mutants:

- zero mutations from list: 100% response rate
- one mutation from list: 100% response rate
- two mutations from list: 80% response rate
- three mutations from list: 40% response rate
- four or five mutations from list: 0% response rate



The number of other active drugs in the regimen also predicted a 1-log response ($P = 0.0012$), as did the number of previous PIs ($P = 0.04$). In people with three or more mutations from Marcelin's menacing seven, none with no other active drugs responded, 29% with one active drug responded, and 60% with two or three active drugs responded ($P = 0.024$).

Inhibitory quotients—which factor measures of resistance and drug levels—remain a much-mulled metric of virologic response. Isabelle Pellegrin (Bordeaux University Hospital, France) brandished a genotypic inhibitory quotient (GIQ)—which uses a mutation set for the resistance measure—to plot response to ATV/RTV in 90 people who had tried a PI (91%) and/or a nonnucleoside reverse transcriptase inhibitor (NNRTI) (62%) before beginning ATV/RTV with a median RNA load of 3.8 log copies/mL (about 6,300 copies/mL) [abstract 8]. They had taken a median of five earlier regimens.

Defining response cutoffs for drugs used in salvage regimens necessarily rests on some messy assumptions—like what constitutes virologic success. Certain savants argue for a response continuum rather than black-and-white cutoffs.

After six months of boosted RTV, the median load dipped 1.2 log copies/mL, and 76% of the study group had fewer than 400 copies/mL. Pellegrin counted 66% as virologic responders with a six-month viral load below 50 copies/mL.

Using the 14-position ATV/RTV resistance score of the French national AIDS trial group (Agence Nationale de Recherches sur le SIDA [ANRS]), Pellegrin found that people with fewer than six of these mutations trimmed their viral load by a median 1.7 log copies/mL, while the median load crept up 0.01 log copies/mL in people with six or more mutations ($P = 0.01$). While 75% with fewer than six mutations qualified as responders, only 20% with six or more mutations met the response criterion ($P = 0.002$). The six-mutation cutoff predicted a six-month response with a specificity of 95% but a sensitivity of only 35%.

Univariate analysis sorted out two mutations not on the ANRS list that foretold a six-month load still above 400 copies/mL—I62V ($P < 0.05$) and V77I ($P < 0.2$). At the same time none of Pellegrin's nonresponders had the ANRS mutations at protease site 36, 63, or 71. And the potential resistance hot spots Marcelin proposed—at positions 16, 60, and 85—did not rank in Pellegrin's analysis.

Pellegrin figured GIQ as ATV trough divided by the number of mutations in the ANRS inventory. By this calculus 88% of people with a GIQ above 0.33 had a sub-50-copy load at six months versus 50% of those with a GIQ under 0.13 ($P = 0.03$). These GIQ limits predicted response with 91% sensitivity but only 36% specificity.

Atazanavir trough, peak, or area under the curve did not correlate with six-month response. But 80% of people with a mutation score below six and a trough above 0.7 µg/mL had a six-month load under 50 copies/mL compared with 47% whose trough lay below 0.2 µg/mL.

What can clinicians make of these diverse response divinings? Or need they fuss about them at all? Atazanavir/RTV has emerged as a favored first-line option, noted Douglas Richman (University of California, San Diego). And research retailed at the workshop (see abstract 29 below) and earlier suggests it lacks the punch of LPV/RTV in people with PI experience. So these doughty efforts to define response cutoffs may seem wasted effort.

Even among clinicians considering an ATV/RTV rescue regimen, suggested Jonathan Schapiro (National Hemophilia Center, Tel Aviv), cutoffs conjured so far may find few takers. Because these three studies—and in fact all efforts of this ilk—rest on arbitrary response definers, the resulting cutoffs retain a random hue. Different definitions of success, Schapiro proposed, would yield different cutoffs.

ViroLogic's Coakley did not dispute this assessment. Whenever research tries to nail down response thresholds, some caprice creeps in. Nothing makes this point more clearly than the largish proportion of people above or below discovered cutoffs who wrong-headedly respond or fail to. In Coakley's study 23% with baseline susceptibility to ATV under the desired 5.2-fold cutoff did not notch a 24-week load below 400 copies/mL. The dismal specificity in Pellegrin's GIQ reckonings, and the flaccid sensitivity in her six-mutation score, do not inspire confidence.

Such uncertainties moved the University of Pittsburgh's Mellors to urge defining a continuum of probability for salvage responses, rather than defining cutoffs. Cut points, he maintained, "are grossly misunderstood by clinicians." But if clinicians find cut points tricky, others observed, they will find probability curves opaque.

The population studied represents another fraught variable in sleuthing down response predictors. Daniel Kuritzkes (Brigham and Women's Hospital, Boston) argued, for example, that the moderately resistant groups Coakley analyzed may not be the best grist for multivariate mills. Differences between Marcelin's and Pellegrin's cohorts could explain why certain novel mutation candidates popped up in one study but not the other.

Of course the vagaries these studies spotlight in guesstimating success apply not only to ATV/RTV but to any antiretroviral prescribed for people with resistant virus.

Atazanavir/ritonavir versus lopinavir/ritonavir: Act I, Scene 2

Researchers from the US Food and Drug Administration (FDA) divulged the fastidious analysis behind approval of ATV, focusing on total and individual mutations that felled the once-daily PI in the Bristol-Myers Squibb trial comparing ATV/RTV with LPV/RTV [abstract 29]. At least two regimens had failed enrollees in this 48-week study, and 46% had reduced viral susceptibility to one or more PIs. Before randomization, equivalent proportions in each treatment arm had virus sensitive to ATV and LPV.

After 48 weeks no one with five or more protease mutations responded to ATV, the FDA's Lisa Naeger reported, in an analysis using the agency's time to loss of virologic response (TLOVR) criterion at the 400-copy threshold. But 28% with five or more mutations responded to LPV/RTV. Response rates proved similar in the two groups among people who began the boosted PIs with fewer than five mutations.

Certain mutation clusters undermined ATV/RTV more than others:

- Response to ATV/RTV was weaker in people with *three or more* PI mutations including one of the following: M36I, M46I/L/V, G73S/A/C, V82A/F/T/S, I84V, L90M.
- Response to ATV/RTV significantly lagged response to LPV/RTV in people with *three or more* PI mutations including one of the following: G73S/A/C, I84V, L90M.
- Only 23% of people with L90M responded to ATV/RTV, but L90M appeared to imperil ATV/RTV only when it appeared at baseline with *two or more* other mutations.
- Mutations at positions 48, 54, and 84 deflated response to ATV/RTV, but mainly if any of them appeared as one of *three or more* baseline mutations.
- Response to LPV/RTV outdid response to ATV/RTV in people with *three or more* mutations including changes at positions 36, 71, 73, 84, 86, or 90.
- Response to LPV/RTV proved better in people with one or two mutations at the following positions versus *three or more*: 36, 46, 71, 77, 82, or 90.

Three studies came up with different mutation sets that threaten ATV/RTV in people with PI failures. But they (mostly) agreed that mutations at sites 10, 33, 46, 84, and 90 all flash a bright danger signal.

Baseline fold change in susceptibility also discriminated between responses to these two boosted PIs. People with less than a five-fold change in susceptibility to either ATV or RTV had equivalent responses to the two drugs. But people with more than five-fold resistance at baseline did better with LPV/RTV.

To sum up the ATV reports (on a sour note), three studies fashioned three discouragingly distinct sets of mutations that undercut this PI's antiviral vigor (Table 1). Yet at least two of three research teams saw trouble with mutations at five positions, marked in **bold type**. Substitutions at site 46 signal sure peril for ATV/RTV. When joined by other mutations, these studies and others suggest, the L90M flip may be the king of PI cross-resistance.

Table 1. **Proposed lists of dangerous pre-ATV/RTV mutations**

Swiss-French (Marcelin, abstract 7)	*French (Pellegrin, abstract 8)*	*FDA (trial AI424-045) (Naeger, abstract 29)*
10F/I/V	**10F/I/V**	—
16E	—	—
—	24I	—
33I/F/V	**33I/F/V**	—
—	—	36I
46I/L	**46I/L**	**46I/L/V**
60E	—	—
—	62V	—
—	—	73S/A/C
—	—	82A/F/T/S
84V	—	**84V**
85V	—	—
—	**90M**	**90M**

Sources: Genevieve Marcelin, abstract 7; Isabelle Pellegrin, abstract 8; Lisa Naeger, abstract 29.

GIQ and resistance score for fosamprenavir/ritonavir

French researchers carried their GIQ campaign to a salvage study of fosamprenavir (FPV)/RTV in 100 people who tried a median of 10 earlier regimens including four with a PI [abstract 31]. Pellegrin and Bordeaux University Hospital colleagues tested the merits of the ANRS resistance score for FPV/RTV, which blackballs this boosted PI for anyone with six or more mutations from a set spelled out in Table 2. That list, Pellegrin's results suggest, may not be the surest guide to salvage with FPV/RTV.

The cohort started 700/100 mg of FPV/RTV twice daily with a median of three major PI mutations (interquartile range [IQR] 0 to 4) and a median FPV/RTV score of 4 (IQR 1 to 5). The median viral load stood at 4.8 log copies/mL (about 63,000 copies/mL), and the median CD4 nadir lay at 100 cells/mm^3. After 12 weeks of FPV/RTV 25% had a viral load below 50 copies/mL, 37% had fewer than 400 copies/mL, and 33% had at least a 1-log viral load dip.

Mutations that correlated with 12-week response did not mirror the ANRS list (Table 2). Yet these discrepancies at least partly reflect the study design, which banned people with six or more of the ANRS mutations.

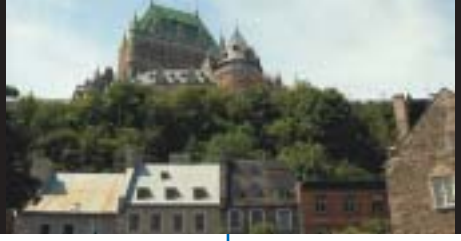


Table 2. **Mutations linked to poor FPV/RTV salvage response**

*ANRS**	*Pellegrin results†*
L10F/I/V	L10F/I/V
K20M/R	—
V32I + I47V or I50V	—
—	L33F/I/V
E35D	—
R41K	—
—	M46I/L
I54V	I54L/V
L63P	L63P
—	A71I/V/T
V82A/F/T/S	V82A/F/T/S
I84V	—
—	L90M

*ANRS proscribes FPV/RTV for anyone with six or more of these mutations.
†Correlated with poor 12-week response.
Source: Isabelle Pellegrin, abstract 31.

In a univariate analysis Pellegrin and colleagues found that nearly any venomous variable one can imagine predicted a poor 12-week response to FPV/RTV—number of previous regimens; viral load zenith; earlier treatment with PIs and NNRTIs; number of NRTI mutations; number of minor, major, or total PI mutations; four or more mutations from the newly defined octet; FPV trough, peak, or 12-hour exposure; and low GIQ (trough/number of FPV/RTV mutations).

Pellegrin did not offer a multivariate analysis, but she proposed three cutoffs for a 12-week response:

- Four or more mutations from the defined set (85% sensitivity, 75% specificity)
- Fosamprenavir trough below 1.8 µg/mL (77% sensitivity, 61% specificity)
- Genotypic inhibitory quotient below 0.6 (77% sensitivity, 61% specificity)

The sensitivity and specificity quotients suggest a bare mutation count foretells success better than FPV level alone or FPV level divided by mutation score (the GIQ). Results like these underlie some researchers' sense that GIQ has little use in the clinic.

GIQ—the genotypic inhibitory quotient—remains a suspect predictor of salvage response. A study of FPV/RTV suggested a homely list of mutations foretells response better than the fancier GIQ.

Keeping score with 21 tipranavir mutations

Atazanavir/RTV cleanly won the workshop sweepstakes for most-pondered salvage PI, though most prefer it for up-front duty. The PI devised, tested, and licensed for salvage, TPV, made do with one useful poster, a shot at defining genotypic and phenotypic cutoffs by Hernan Valdez (Boehringer Ingelheim) [abstract 27].

Valdez began with a bulky data set rolling together people who took TPV/RTV as their only PI in four trials—the two phase 3 RESIST studies of enrollees with triple-class resistance in whom two PIs had flopped but with two or fewer mutations at positions 33, 82, 84, and 90; a companion trial for people with more than two mutations at those sites; and a phase 2 dose-finding study with no entry limits involving positions 33, 82, 84, or 90.

This analysis aimed to test Boehringer Ingelheim's busy mutation list of 21 substitutions at 16 positions—10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, and 84V. But along the way Valdez turned up evidence that baseline fold change in susceptibility to TPV predicted at least a half-log nip off viral loads during the RESIST trials' first eight weeks.

Among 252 people with less than threefold resistance at baseline, 233 (92%) met the modest half-log response benchmark. Yet a hefty proportion with higher baseline resistance—74 of 109 (68%)—also enjoyed a half-log viral load ebb. The significantly better response in the group with lower baseline resistance ($P<0.001$) did not depend on cotreatment with the fusion inhibitor enfuvirtide (ENF).

Using the same eight-week half-log response marker, Valdez confirmed that more mutations from Boehringer Ingelheim's laundry list chip away at chances of viral control:

- Of 239 people with two listed mutations, 225 (94%) responded.
- Of 446 people with three to five listed mutations, 374 (84%) responded.
- Of 60 people with six or more listed mutations, 43 (72%) responded.

People with up to three of the 21 menacing mutants managed a reasonable response after 24 weeks of TPV/RTV (Table 3). The response rate slipped sharply when four or more listed mutations accrued. People with eight or more of the 21 mutations had essentially no response.

Boehringer Ingelheim's 21-mutation-long agglomeration steamed even resistance mavens with steel-trap minds and typify the "data quagmire" Mellors complained about. Many note that the list omits L90M, a founding member of Boehringer Ingelheim's "universal" quartet of minatory mutants. Douglas Mayers, the company's viral chief, reasonably concurs that L90M thwarts TPV as surely as it does other PIs; it merely failed to emerge in the statistical analysis that crowned the 21.

Everyone yearns for further work that may narrow the lineup of usual suspects in resistance to this PI. But the dreaded 21 may yet prove a bellwether of 21st-century resistance reckonings.

Table 3. **Week 24 viral load change according to mutation score**

Mutations	*Patients*	*Median RNA drop (log copies/mL)*	*Interquartile range (log copies/mL)*
0 to 1	114	2.10	-0.82 to -2.77
2 to 3	242	0.89	-0.21 to -2.35
4 to 5	260	0.45	-0.03 to -2.15
6 to 7	68	0.49	-0.03 to -1.60
8 or more	4	0.08	+0.01 to -0.18

Source: Hernan Valdez, abstract 27.

NUKES, TAMs, AND TALISMANS

Resistance to NRTIs seems at once utterly transparent—M184V and lamivudine (3TC), the TAMs and zidovudine (AZT)—and terribly turbid—what K65R or L74V does to TAMs, what TAMs do to stavudine (d4T). Anyone feeling confident in a growing grasp on resistance to NRTIs had that grasp greased in Québec.

Rating an array of algorithms for how well they prophesy responses to ABC or ddI, a brain trust of resistance experts discovered—to the dismay of all—that nearly every algorithm widely missed the mark.

Defining resistance to abacavir and didanosine

First up in the foray into NRTI resistance was Dominique Costagliola (Pierre and Marie Curie University, Paris), proxy for a consort of experts assembled by the Forum for Collaborative HIV Research [abstract 9]. This team set out to trace the tendrils linking genotype-based algorithms with virologic outcome [see note 4]. They picked ABC and ddI as guinea pig pills because resistance to the first seems straightforward and to the second sinuous. But they ended up finding that everyday algorithms didn't predict responses to either drug consistently.

The analyses involved treatment-experienced people from nine databases in North America and Europe—583 people with a pre-ABC viral load of 4.4 log copies/mL (about 25,000 copies/mL) and an average 1.6-log change after eight weeks of an ABC regimen; and 400 people with a pre-ddI viral load of 4.2 log copies/mL (about 16,000 copies/mL) and a mean 1.8-log viral load change after eight weeks of a ddI combo. No one in the ABC analysis used that NRTI before, and no one in the ddI study had tried ddI.

The Forum for Collaborative HIV Research experts devised regression models fixed on eight-week change in viral load, comparing resistant virus with intermediate-resistant or sensitive virus. They adjusted the models for baseline viral load and number of active drugs in the regimen. This eight-week scrutiny will be followed by a 24-week analysis.

Catechizing eight algorithms, Costagliola discovered that predicted mean changes in viral load for ABC-resistant versus -sensitive virus ranged from -0.02 to +0.66. The gap between predicted mean changes in viral load for intermediate-resistant versus sensitive virus yawned almost as widely, from +0.10 to +0.64.

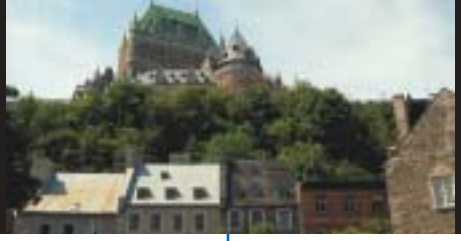
Univariate analysis of the eight algorithms confirmed displeasingly disparate correlations between intermediate or sensitive virus and mean change in viral load. For five of these eight algorithms, Costagliola found no significant correlation between change in viral load and viral susceptibility. This statistical cross-exam did suggest that mutations at positions 70 and 215 would best be dropped from rules for interpreting resistance to ABC.

Algorithm reliability grew gloomier with the six systems used to predict response to ddI. The range for mean change in viral load for sensitive versus resistant virus proved tighter than with ABC (-0.12 versus +0.28). But univariate analysis found no correlations between change in viral load and viral susceptibility for *any* of the algorithms tested.

Dismayed, Costagliola and colleagues tossed out the whole data set and plugged in numbers from 300 people in the NARVAL resistance test trial.[5] They picked the NARVAL data because the trial enrolled people with and without ddI or ABC experience. That meant the study population was more heterogeneous than the original cohorts in baseline resistance to either drug. The researchers reasoned the more diverse NARVAL cohort might prove more fertile ground for validating the algorithms.

With the NARVAL data set the mean change in viral load for resistant versus sensitive virus narrowed considerably (+0.36 to +0.52). And univariate analysis figured significant correlations between viral load change and viral susceptibility for three of the six algorithms.

This brave inquest into algorithmic riddles left some attendees slack-jawed. The University of California, San Diego's Richman , a founding father of HIV resistance research, went so far as to wonder whether clinicians can rely on algorithms at all—given the gaping predictive variability Costagliola confirmed. She countered that further analysis—with further expansion of the data set to include more people already treated with ddI or ABC—may resolve some discrepancies.



Nancy Shulman (Stanford University, Stanford, California) and US AIDS Clinical Trials Group (ACTG) colleagues tackled the troubling question of resistance to ddI by retrospectively pooling data from 444 NRTI-experienced people enrolled in five ACTG trials [abstract 49].

They used data from three trials to indict likely resistance mutations by stepwise regression analysis. Then they probed the merits of their picks by comparing baseline mutations with RNA results in two trials of ddI *monotherapy*—ACTG 173 and ACTG 307. They also aimed to figure how much individual mutations contribute to viral susceptibility to ddI.

The resistance score they settled on summed mutations at nine positions: Substitutions at reverse transcriptase sites 43, 67, 74, 75, 184, 210, 215, and 223 contributed to resistance, while a mutation at position 83 lessened resistance. This score correlated strongly with fold-change in susceptibility to ddI ($r = 0.67$, $P < 0.0001$).

Next Shulman compared the ACTG score with the formula based on four-week viral load change in the Jaguar trial of add-on ddI[6] (41L + 67N + 69D + 74V + 215Y/F + 219Q/E – 70R – 184V). The ACTG score with the position 184 mutation ($r = 0.43$, $P = 0.002$) or without 184 ($r = 0.41$, $P = 0.005$) tracked with virologic response more closely than the Jaguar score ($r = 0.25$, $P = 0.09$).

Antagonism between the K65R mutation and TAMs may prove more than a neat trick that delights resistance pooh-bahs, two studies suggested. But those studies were small, and the K65R-TAM nexus needs more work.

What thymidine analog mutations do to K65R

The TDF-evoked K65R mutation and TAMs (M41L, D67N, K70R, L210W, T215F, and K219Q) are coequal members of a mutual abomination society that renders their coexistence (nearly) impossible. Viral clones forced to carry both K65R and TAMs are less resistant to AZT than TAM-only mutants—and less resistant to TDF and ABC than K65R-only mutants. Urvi Parikh (University of Pittsburgh) showed how K65R gums up the cogs that click AZT resistance into place.[7] But how do TAMs relieve resistance conferred by K65R?

In experiments designed to find out, Parikh reckoned kinetics for single nucleotide incorporation of AZT triphosphate (TP), deoxyadenosine triphosphate (dATP), and tenofovir diphosphate (TFV-DP) in reverse transcriptase of:

- Recombinant wild-type (WT) virus
- K65R
- "TAM 41": M41L, L210W, and T215Y
- K65R/TAM 41: K65R plus M41L, L210W, and T215Y
- "TAM 67": D67N, K70R, T215F, and K219Q
- K65R/TAM 67: K65R plus D67N, K70R, T215F, and K219Q

Parikh found that K65R heightened selectivity against TFV-DP by decreasing incorporation without affecting binding. TAM 67 reverse transcriptase antagonized K65R by restoring incorporation of TFV-DP. TAM 41 also antagonized K65R—but less than TAM 67—by bridling selectivity for dATP versus TFV-DP. K65R also more than doubled selectivity against AZT-TP [abstract 85].

Can clinicians exploit the mutual antagonism of K65R and TAMs? It seems so, two workshop studies suggested, but how mutant virus manifests its wiles in humans always trumps the tangles that lab work may tease apart. For example, Parikh's paradigm suggests that K65R would have a tough time emerging during failure of a regimen combining AZT and TDF. And that would be a good thing since K65R renders virus less susceptible all NRTIs *except* AZT.[8] Bernard Masquelier (Bordeaux University Hospital, France) put that theory to the test in a nonrandomized trial enrolling 24 treatment-naive people starting AZT/3TC (as Combivir) plus TDF [abstract 20].

This group began their triple nukes with a median viral load of 4.3 log copies/mL (about 20,000 copies/mL) and median CD4 sum of 443 cells/mm^3. Masquelier searched for resistance mutations in RNA and proviral DNA before treatment and six months into therapy. Despite this group's naive status, five people had TAM-tainted virus—four with T215D/C and three with M41L.

Three people stopped treatment or switched to another regimen before month six. An intent-to-treat analysis set the six-month sub-50-copy rate at 63%, and an on-treatment analysis figured an 83% response rate. Masquelier recorded four rebounds from below 50 copies/mL. No new resistance mutations arose in three of these people, but K65R cropped up in one. That meant K65R appeared in 4% of people overall but in 25% of rebounders. So AZT does not hoist a shield impervious to K65R. But the antiviral vigor of this three-NRTI mix against TAM-laden virus bears notice.

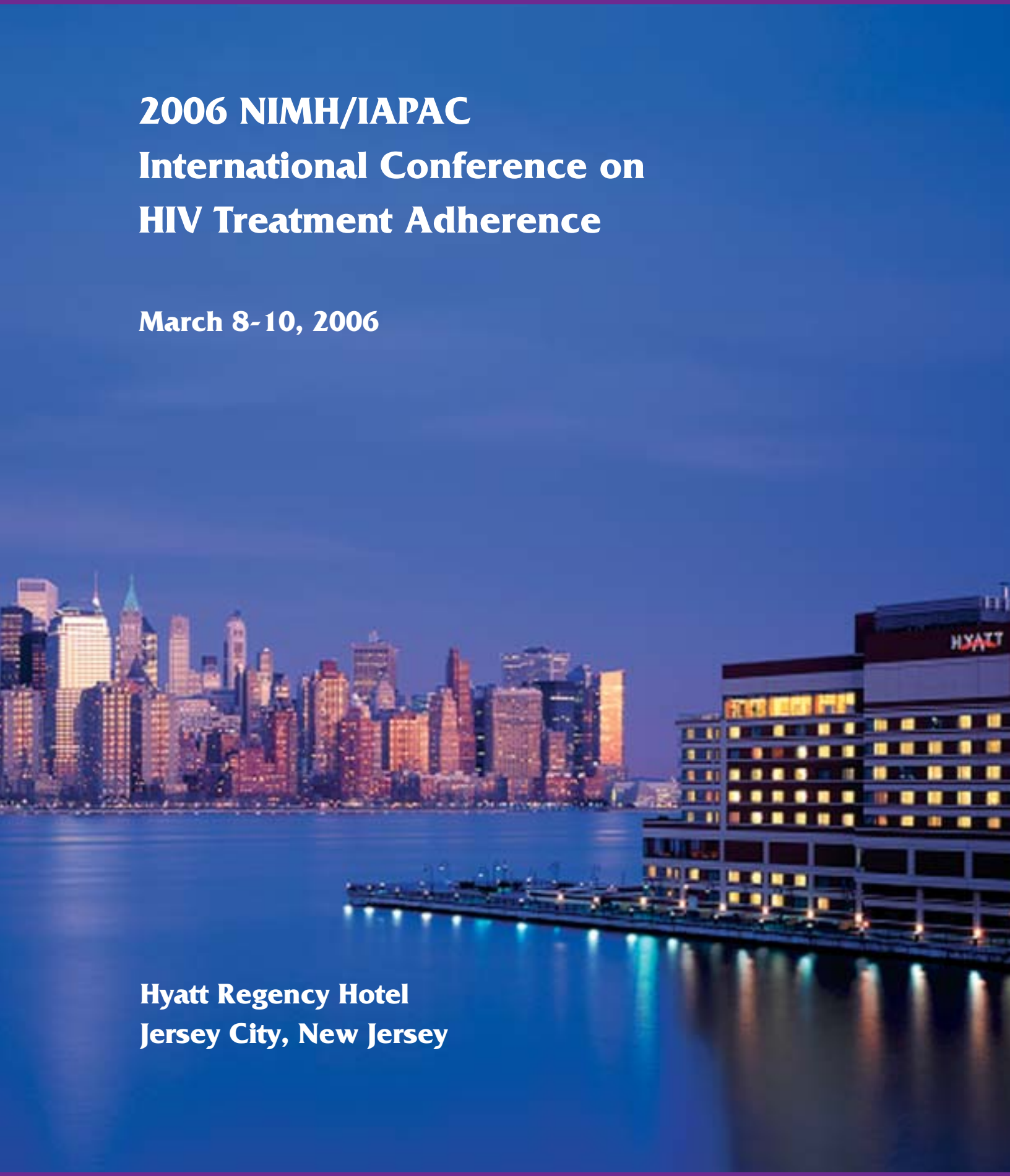
In a study outlined in the workshop abstract book but not posted at the meeting, Schlomo Staszewski (JW Goethe University Hospital, Frankfurt) found that AZT can handcuff virus carrying K65R but no TAMs [abstract 17]. He outlined three case reports of people who added only AZT to a failing regimen and kept taking their other drugs. All three smartly pushed their viral load beneath 50 copies/mL, even though their TAM-less virus bore mutations conferring resistance to all other drugs they continued.

K65R and multiple TAMs almost never share the same viral genome. Earlier work by Parikh found K65R and T215Y/F plus two other TAMs rubbing genomic shoulders in only 24

Call for Abstracts

2006 NIMH/IAPAC International Conference on HIV Treatment Adherence

March 8-10, 2006



Hyatt Regency Hotel
Jersey City, New Jersey

Submission deadline: October 14, 2005

Goal

To provide a forum where the state-of-the-science for HIV treatment adherence research will be presented, discussed, and ultimately translated into evidence-based approaches that make a difference in real-world clinical and community settings, both in the United States and internationally. Human service, health care, and behavioral science professionals and practitioners will examine scientifically sound and practical strategies to enhance adherence to HIV treatment in a variety of settings. Participants will have the opportunity to share ideas about improving adherence to antiretroviral regimens at this international conference; we seek to strengthen collaborations among government agencies, program practitioners, and researchers.

Objectives

After attending this conference, participants will possess the following skills:

- Identify factors related to substance use, mental health, and social factors that you can assess to determine non-adherence
- Describe adherence assessment tools and identify the approaches that are relevant to the patients you serve
- Identify interventions to improve adherence that can be integrated into your patient care
- Describe factors that influence adherence, including access to health care providers, patient education approaches, and culturally-sensitive program design
- Identify aspects of health care delivery programs, including clinician characteristics, that promote your patients' adherence
- Identify specific antiretroviral treatments that affect adherence in your specific patient populations

Abstract submissions

Understanding and improving adherence to HIV treatment is a complex, multi-level issue that involves factors at the societal, community, structural, systems, provider, biological, and individual level—across the lifespan of all patients living with HIV/AIDS. Moreover, these factors often interact, and call for a multidisciplinary research approach. Therefore, this Call for Abstracts invites a broad range of topics for the conference. The following topics are meant only to serve as examples for submission areas.

Abstracts may address substance use issues and impact, mental health issues, housing and social stability, adherence assessment and promotion tools, adherence interventions, ethnic disparities, the intersection of adherence and prevention issues, operational and system-level factors, patients in remote or rural locations, or other contextual factors. Other broad areas may include provider training, cultural sensitivity, patient-provider communication, clinic flow, regimen characteristics, and retention in care. Abstracts also can address adherence as it impacts and is impacted by physiology, pharmacokinetics, and viral resistance. Abstracts that address the unique challenges in resource-limited settings are encouraged.

All submitted abstracts will be considered for oral and poster presentations. All abstracts accepted for oral presentations also will be displayed as posters. Late-breaker abstracts will be accepted, but not for oral presentation. All submitted abstracts should report information not previously published, or intended to be published, prior to March 8, 2006.

Dates to remember

Abstract submission deadline — October 14, 2005
Abstract disposition deadline — November 30, 2005
Late-breaker abstract deadline — January 17, 2006

Registration information will be available shortly.

Abstract submission guidelines

Abstracts must be submitted in one of the following two formats:

Format A:

1. All authors should be listed as follows: last name, first initial, institution, city, state;
2. Title of abstract;
3. Background: a concise statement of the issues evaluated;
4. Methods: the investigational model used;
5. Results: specific findings; and
6. Conclusions: summary of findings that are supported by results.

Format B:

1. All authors should be listed as follows: last name, first initial, institution, city, state;
2. Title of abstract;
3. Issues: a short summary of issues addressed by the abstract;
4. Description: a brief description of the project, experience, or intervention;
5. Lessons learned: a brief description of project results; and
6. Recommendations: further recommendations or next steps.

When submitting an abstract:

1. All abstracts must be submitted in English.
2. The deadline for submissions is October 14, 2005.
3. The author is responsible for all grammatical and factual details. No revisions will be accepted after the initial submission.
4. **Abstracts should be submitted to abstracts@IAPAC.org.**
5. The main author will be notified by e-mail of abstract receipt.
6. Notification of abstract disposition will occur by November 30, 2005.
7. Late-breaking abstracts will be accepted. The deadline for late-breakers is January 17, 2006.
8. All abstracts should use Times Roman font, sized 10 to 12 points, single-spaced. The body is limited to 2,000 characters including spaces. The conference cannot guarantee that tables, graphs, or visual items within the body of the abstract will be optimally reproduced.

Abstracts are considered official communication to the conference. For accepted abstracts, submitters agree to attend the conference and present abstracts as scheduled. Accepted abstracts will be published in the conference proceedings. Submission of an abstract implies permission to publish if accepted.

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of more than 56,000 viral isolates tested.[9] But K65R and TAMs—with the possible exception of codon 215 changes—cohabitate quite cheerfully in people with ample NRTI experience. Andrew Nevins (Stanford University, Stanford, California) confirmed that matrimony in a retrospective study of 39 much-treated people whose virus carried K65R [abstract 16].

Sixteen of the 39 (41%) had at least one TAM, and five had three or more. But no one had T215Y/F. K65R appeared linked to familiar TAMs at positions 41, 67, 70, 210, and 219, although only cloning can verify those links. People who also had the M184V mutation and those whose new regimen had a higher genotypic susceptibility score had the best chance of reaching a sub-50 viral load with salvage therapy. But no other factor tested predicted a better salvage response—including AZT, TDF, or any other specific drug in the salvage regimen, or a new class of drugs in the new regimen. Nevins cautioned the study may be too small to confirm or rule out the impact of such variables.

Several workshop reports addressed two pesky questions about CCR5 antagonists—without always reaching the same answer: Will cross-resistance or coreceptor switching undercut responses to this catchy new class?

Tangled feet on TAM pathways

Sifting TAMs for nearly two decades convinces some experts they can sort these mutations into two clusters:

- TAM-1 consists of M41L, L210W, and T215Y
- TAM-2 features D67N, K70R, T215F, and K219Q/E

Does the path taken make a clinical difference? It depends on whom you ask. Separate studies at the 2005 Conference on Retroviruses and Opportunistic Infections hinted that 3TC ties up TAM-2 mutants better than emtricitabine (FTC),[10] an edge perhaps also held by d4T over AZT.[11] But a TAM-path sortie by the UK Collaborative Group on HIV Drug Resistance found the TAM topography so choked with overlapping paths that mapping only two seemed "simplistic" [abstract 130].

Threshing through 2,379 genotypes of treatment-experienced people, David Dunn (MRC Clinical Trials Unit, London) discovered 116 distinct TAM patterns, none of which looked much like a well-toed path. He traced only 12 patterns that made up more than 2% of the trails plotted.

TAM-1 mutations turned up in 728 tests (31%) and TAM-2 mutations in 685 (29%). Mutations from *both* TAM bins littered far more genotypes—956 (40%). Indeed, the most common single mutation covey—at a prevalence of 14%—consisted of three TAM-1 mutants (M41L, L210W, and T215Y) plus one TAM-2 interloper (D67N).

What do you call *that* mutant array, wondered TAM trailblazer Brendan Larder. More than 10 years of clinical work show it's a nasty virus—and the Collaborative Group survey confirmed it's a favored route. But you can't call it TAM-1 or TAM-2. Kuritzkes of Brigham and Women's Hospital, on the other hand, still sees some merit in the TAM-path distinction, though he thinks it remains unvalidated.

CCR5 ANTAGONIST ANGST

Absent outrageous fortune, CCR5 antagonists will become the next class of antiretrovirals. But at this late stage of development, two irksome questions about these drugs still chafe:

- Will HIV become cross-resistant to CCR5 antagonists?
- Will CCR5 antagonists drive HIV to CXCR4 coreceptors?

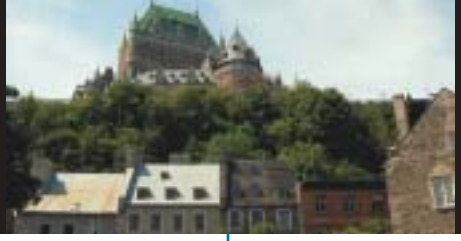
A few studies at the Resistance Workshop offered contradictory answers.

Julie Strizki (Schering-Plough) had good news and bad news about two CCR5 compounds labeled SCH 351125 and SCH 417690 (SCH-D or vicriviroc) [abstract 59]. The good news is that resistance to these agents evolves at a plodding pace—in the lab. The bad news came in two flavors: Virus resistant to Schering's antagonists proved cross-resistant to other offerings in this class, and one resistant species appeared to favor CXCR4 as readily as CCR5.

Serial passage studies with the Schering-Plough antagonists showed that resistance emerged slowly as mutations in gp120 accrued. Resistant virus did not surface at all for up to 16 weeks in some passage studies. Clonal analysis traced most mutations to gp120's V3 loop, but Strizki could find no V3 mutations in some resistant virus. That suggested undiscovered mutations outside gp120 may also hamstring the Schering-Plough drugs.

HIV resistant to the SCH hopefuls remained susceptible to AZT, FTC, and indinavir (IDV). But Strizki confirmed their cross-resistance to other Schering CCR5 antagonist compounds and to a Merck CCR5 drug. She also found that the CXCR4 inhibitor AMD3100 did not stifle replication of virus resistant to Schering-Plough's CCR5 antagonists—good evidence that these mutants did not swap coreceptor preference and begin homing to CXCR4. But certain escape mutants grown in X4 cells retained their R5-linking talents, a dismaying development suggesting dual (X4 + R5) tropism.

Unlike Strizki, Pfizer's Mike Westby saw no signs of cross-resistance in studies of maraviroc, the CCR5 plugger



formerly tagged UK-427,857 [abstract 65]. He cooked up four clones from maraviroc-resistant virus and confirmed that they retained resistance to the Pfizer drug. Then he tested the clones' susceptibility to three CCR5 antagonists—Schering's SCH-C and SCH-D (vicriviroc) and GlaxoSmithKline's GW873140—and to the fusion inhibitor ENF and the PI saquinavir (SQV). All four clones remained sensitive to these drugs with less than a five-fold gain in 50% inhibitory concentration. This retained susceptibility, Westby observed, indicates these mutants also retain their CCR5 tropism.

Molecular modeling by the Pfizer team showed that maraviroc, SCH-C, SCH-D, and GW873140 nestle into the same CCR5 pocket. But they sit there in slightly different postures. Westby proposed these subtle yaws in binding conformation explain the lack of cross-resistance. But in a workshop colloquy on CCR5 research, he cautioned that his findings do not rule out cross-resistant blossomings in clinical trials.

Painstaking experiments by Donald Mosier (Scripps Research Institute, La Jolla, California) may soothe some jumpy nerves among CCR5 drug developers [abstract 60]. His results suggested that fears of receptor switching as a resistance gambit against CCR5 antagonists "may be overstated."

Two groups offered evidence against R5-to-X4 coreceptor switching during CCR5 antagonist therapy. But these crafty efforts do not put to rest the possibility that a zesty CCR5 drug may make an R5 virus switch allegiance to X4.

Mosier used site-directed mutagenesis to mint all 32 possible "mutation intermediates" in the sesquipedalian sequence leading from R5 to X4 virus. Then he sized up these mutants to see how well—or poorly—they invaded CCR5- and CXCR4-expressing target cells and how sensitive they were to the CCR5 inhibitor PSC-RANTES.

Figuring that the 32 mutants offered 120 viable routes from R5 to X4 tropism, Mosier found only four (3%) of those routes "operational." Yet given HIV's polymorphous perversity, four tracks from R5 to X4 may be four too many.

GlaxoSmithKline, a third aspirant in the dash to market a CCR5 meddler, sent Kathryn Kitrinos to the workshop with another mote of evidence arguing against resistance by coreceptor switching [abstract 61]. Her work focused on a person who took the lowest dose of GW873140—200 mg once daily—in a dose-ranging study of the drug.

Samples gleaned at screening and on treatment day one contained virus with an exclusive preference for the CCR5 coreceptor. But virus collected on treatment day 10 readily snagged either CCR5 or CXCR4. On the 24th and last treatment day, this person's virus seemed to shed its X4 tropism and again home solely to CCR5.

But as all resistance savants now know, standard assays see only those species that make up about 20% or more of a person's viral pool. Deploying a more discriminating assay to size up virus cloned from these samples, Kitrinos confirmed dual tropism for X4 and R5 in one of 23 clones (4%) as therapy began, six of 22 clones (27%) on treatment day 10 (when the standard assay spotted dual tropism), and two of 24 clones (8%) on day 24.

In other words this person's viral horde had a thin sprinkling of CXCR4-tropic species before treatment with GW873140 ever began. That tiny population burgeoned to detectable levels during the first week of therapy, then waned to its original penny-weight proportions. Comparing gp160 sequences of sampled virus by phylogenetic analysis, Kitrinos bolstered her contention that dual-tropic variants arose from virus lurking in scant pretreatment caches.

This careful and convincing analysis must be read in the right context. Kitrinos proved GW873140 monotherapy did not drive CCR5-tropic virus into dual tropism—a trait that may spur faster progression by doubling HIV's binding options. The X4/R5 virus remained fully susceptible to the CCR5 antagonist in cells expressing only CCR5 coreceptors.

But these results apply to *one person* taking a low dose of GW873140 unlikely to see clinical use. And even though monotherapy did not engender resistance to the antagonist by selecting X4-favoring mutations, it did (briefly) give wing to a recondite X4 flock. Whether that happens with some frequency when CCR5 antagonists reach the clinical arena—and whether such outgrowth puts progression on a faster flyway—are questions that can't be answered now.

WHO TRANSMITS WHAT WHEN?

Every day the world's priapic populace spurts 16,000 gallons of HIV-sullied semen. And cargoes of the stuff carry drug-resistant virus.

That estimate came from Davey Smith (University of California, San Diego), an earnest young man who did not blush at his bold report (detailed below). Like most researchers in this field, Smith must be inured to mankind's Dionysian mold, the progenerative drive that ensures survival of the species—human and viral. And now that imperfect antiretrovirals taken by impassioned people guarantee resistance, the risk of transmitted mutants imperils sex partners and needle sharers alike.

Rigging an epidemiologic model to factor treatment uptake and response, Andrew Leigh Brown (University of Edinburgh) analyzed prevalence of primary infection with resistant virus and transmission of drug-resistant HIV in a San Diego cohort [abstract 115]. The model predicted declining rates of primary resistance only if fitness of transmitted virus drops over time. If fitness of resistant virus stays steady, rates of infection with resistant virus will billow "continuously." Without sharp-eyed screening for transmitted resistance, Leigh Brown warned, "uncontrolled primary resistance and treatment failure" will ensue.

And freshly transmitted resistant virus ends up not only in semen, but also in long-lived cells, according to research by Jade Ghosn (Pitié-Salpêtrière Hospital, Paris) [abstract 161]. With PRIMO cohort colleagues, she figured that resistant strains picked up in primary infection "massively fuel" peripheral blood mononuclear cells (PBMCs).

The study involved 518 people with primary HIV infection, 44 of whom (8.5%) got handed resistant virus. A median 46.5 days elapsed between the estimated date of infection and inclusion in the cohort. In plasma samples Ghosn unmasked NRTI resistance mutations in 27, NNRTI mutations in 13, and PI mutations in 23. Of the 27 people with NRTI mutations in plasma, 21 had exactly the same mutations already hunkered down as DNA in PBMCs. Of the 13 with NNRTI mutants in plasma, 12 had identical sets in PBMCs. And of the 23 with PI mutations in plasma, 18 had the selfsame mutations in DNA.

Yes, using crystal methamphetamine ups the odds of transmitting drug-resistant HIV, one team found. No, dual-tropic, triple-resistant HIV does not get transmitted much, a second group showed. But such triple-witched virus is on the loose.

Crystallized risk of resistance transmission

Common sense says methamphetamine-fed sex probably swells resistance transmission rates. At the workshop Peter Chin-Hong (University of California, San Francisco) offered data to prop that postulate [abstract 117]. He questioned 168 men and 21 women during 1,037 visits (average 5.5) about their sexual exploits and use of crystal methamphetamine and sildenafil (Viagra). All these people had a measurable viral load and at least one resistance mutation while taking antiretrovirals.

During at least one study visit, 29% reported unprotected anal or vaginal sex with a person without HIV or with an unknown HIV status; 6% owned up to unsafe sex with an uninfected or serostatus-unknown partner during more than 75% of visits. Multivariate analysis pinpointed five predictors of unsafe sex with such a partner in the preceding four months at the following odds ratios (OR) and 95% CIs:

- Methamphetamine use: OR 4.2 (1.6 to 11.3), $P = 0.004$
- Sildenafil use: OR 3.7 (1.7 to 8.3), $P = 0.001$
- Younger age (per 10 years): OR 3.2 (1.8 to 5.7), $P < 0.001$
- Depression: OR 1.8 (0.98 to 3.5), $P = 0.06$
- Homelessness: OR 4.7 (0.88 to 24.7), $P = 0.07$

Taking sildenafil and younger age—but not popping crystal meth—raised risks of unprotected sex *only* with HIV-infected partners:

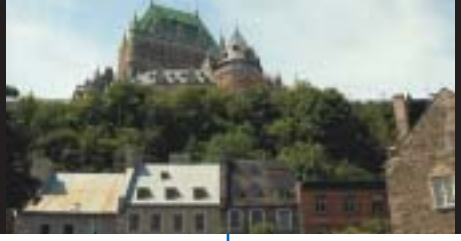
- Sildenafil use: OR 7.3 (2.7 to 19.6), $P < 0.001$
- Younger age (per 10 years): OR 2.2 (1.2 to 4.0), $P = 0.013$

A substantial minority of people, 38%, had mutations conferring resistance to the first three antiretroviral classes, while another 26% had NRTI- and PI-related mutations, 15% NRTI- and NNRTI-educed mutations, and 1% NNRTI- and PI-inspired mutations. But how prevalent is transmission of multidrug-resistant (MDR) virus outside gay hot spots like San Francisco? And how frequent is transmission of MDR virus that can use both coreceptors—like the virus transmitted in the storied New York case?[12]

Ron Kagan (Quest Diagnostics, San Juan Capistrano, California) addressed both questions by analyzing more than 153,000 viral sequences from HIV-infected people [abstract 128]. He charted a drop in rates of MDR HIV, defined as virus bearing mutations engendered by four or more NRTIs, four or more PIs, and one or more NNRTIs. Prevalence of such maculate breeds stood at 12% in 1998, then faded to 10% in 2001 and 2002, and slid all the way to 4.6% so far in 2005. Sequence scrutiny tied the New York dual-tropic virus to 12 other sequences traced to four people in this vast database.

Michael Kozal (Yale University, New Haven, Connecticut) and coworkers at the University of Western Ontario used a looser definition of multidrug resistance—virus resistant to at least one drug in each of the first three classes—in their study of 393 people (56% male, 79% heterosexual) [abstract 127].

Of the 250 people who had sex during the study, 112 (45%) had unprotected anal, vaginal, or *oral* sex, exposing 354 of 1,225 sex partners (29%) to HIV. Thirty-nine people practicing risky sex (35%) did so with drug-resistant virus, including 13 (11.6%) with double-class resistance and two (1.8%) with triple-class resistance. People with resistant virus exposed 71 of 354 partners (20%) to their mutations, 29 of them to double-barreled mutants and two of them to triple threats.



Using the same definition of multidrug resistance, Gayatri Jayaraman (Public Health Service of Canada, Ottawa) tracked a low but abiding rate of transmission to newly infected people [abstract 123]. Of 1,738 just-diagnosed, untreated people studied from 1998 through March 2004, more than 8% had at least one resistance-conferring mutation. Jayaraman first spotted multidrug resistance transmission in 1999 at a prevalence of 0.9%. That rate climbed to 1.9% by 2002 and has stayed there since.

Major transmission of minor populations?

Estimates of double- and triple-class resistance grow if one uses more powerful assays, reported Jeffrey Johnson (US Centers for Disease Control and Prevention [CDC], Atlanta) in a study involving 282 samples gathered from treatment-naive people from 1997 through 2001 [abstract 111]. Sequencing specialists at the CDC refined point mutation assays to probe for pocket-sized populations of L90M in protease and D67N, K70R, and M184V in reverse transcriptase.

Assays that flushed out as little as 0.05% of viral quasispecies boosted the estimate of double-or-greater-class resistance from 12% to 15% and of triple-class resistance from 2% to 4%. And those jumps reflect analysis of only four mutations, including none of the oft-transmitted NNRTI mutations.

Assays that probe otherwise hidden pockets of resistant virus almost invariably document higher transmission rates than standard sequencing. But the reliability of these super-snooping tests remains to be validated.

Karin Metzner (University of Erlangen-Nuremberg, Germany) used similarly acute assays to smoke out wisps of resistant virus bearing L90M, M184V, or K103N (the NNRTI cutthroat) in 49 untreated acute seroconverters [abstract 110]. She found one or more of these mutations in 10 people (20.4%), all at levels that standard sequencing would miss. One person (2%) had L90M, five (10.2%) had K103N, and six (12.2%) had M184V.

Robert Grant (Gladstone Institute, San Francisco) cautioned that researchers must still validate the accuracy of these super-mutant snoopers.

Recent resistance transmission trends

Whether transmission rates of resistant virus are going up, going down, or going sideways depends on how hard—and where—you look. In Denmark and the workshop's host province, Québec, for example, transmission of resistant virus took a slide in the new millennium.

Jan Gerstoft (Copenhagen University) figured transmission risk by reckoning the proportion of treated people with a viral load above 1,000 copies/mL and thus likely to pass along resistant species when infecting another person [abstract 121]. This comprehensive analysis rests on a nationwide cohort of *all* 3,722 Danes seeking medical care for HIV from 1995 through 2003. That group included 2,729 taking a potent antiretroviral regimen.

The transmission risk group—those with a viral load topping 1,000 copies/mL—peaked at 425 in 1998 (24% of people at that point) and tumbled to 233 (9%) in 2003. The relative change over those years measured 0.81 per year ($P = 0.000$). A quick chute in PI failures accounted for most of this improvement. The number of people who endured a PI failure crescendoed at 277 (14%) in 1999 and slipped to 152 (5.9%) in 2003 for a relative change of 0.80 per year ($P = 0.000$). The number of NNRTI failures crested at 119 (4.6%) in 2002, then dipped to 108 (4.2%) by 2003, but this drop was not significant.

Sage antiretroviral policy planning may contribute to this stellar record. Danish clinicians do not advocate treatment interruptions. In 2003 only 6.4% of antiretroviral-treated people were on a drug holiday.

Better responses to antiretrovirals after 2000 may also account for lower recent transmission of resistant species in Québec [abstract 120]. Jean-Pierre Routy (McGill University, Montreal) sorted resistance records of 230 untreated people diagnosed with HIV infection at eight centers from January 1997 through March 2005. Nineteen (8%) had primary drug resistance.

Univariate analysis comparing people infected with resistant and nonresistant virus found no effect of age, gender, ethnicity, education, income, or HIV transmission route. People infected with resistant virus had a higher CD4 count (610 versus 440 cells/mm^3, $P = 0.009$) and a lower viral load (4.12 versus 4.75 log copies/mL, $P = 0.003$) than those infected with wild-type virus. An earlier year of infection also favored primary resistance in the univariate analysis.

Multivariate analysis singled out two independent predictors of infection with resistant virus. Being infected after 2000 cut the risk of resistance 70%, and a lower viral load trimmed the risk 46%.

Treatment response with transmitted mutants

Abstracts of studies on resistance transmission always start with dire forebodings about how people who pick up mutant HIV will do on their first regimen. Yet evidence of poor first-line responses remains surprisingly thin. One workshop study offered some telling clues that starting therapy with inherited mutations puts people at a disadvantage. But in another study the same researchers found no hint of rapid progression among people infected with MDR virus.

The 12% rate of infection with resistant virus in France[13] means more than one in 10 people may start a regimen

including one or more already enfeebled pills. That's what happened to 35 of 45 people (78%) handed resistant virus by a sex or needle partner, reported Marie-Laure Chaix (René Descartes University, Paris) [abstract 114]. She compared them with 259 people in the same two cohorts—all of them infected since 1996.

Of the 35 people with resistant virus, 33 had NRTI mutations, 10 had PI mutations, and three had NNRTI mutations. Chaix did not analyze the 10 people infected with resistant virus who started a regimen containing no mutation-threatened drugs. As in Routy's study of Québecois with primary resistance (see abstract 120 above), *higher* CD4 count and *lower* viral load favored infection with resistant virus in Chaix's cohort.

After six months of treatment 81% in the resistant group versus 95% in the non-resistant group had a viral load below 400 copies/mL ($P = 0.02$). Respective proportions with a sub-50 load were 57% and 79% ($P = 0.02$). At treatment month three people with wild-type virus had an estimated 0.71-log lower viral load than people with resistant virus ($P < 0.01$). When Chaix adjusted the analysis for gender, age, and baseline CD4 count and viral load, people starting treatment without resistant virus had a 0.6-log lower viral load at three months ($P < 0.01$).

Getting infected with resistant virus—then getting treated with mutant-menaced drugs—raised the risk of a suboptimal response after six months, a finding arguing for resistance testing before therapy.

A multivariate analysis adjusted for the same variables plus time since HIV infection determined that infection with resistant virus and a higher baseline viral load independently narrowed the odds of reaching a sub-400 load after three months of therapy (Table 4). Chaix saw a trend toward a better three-month response among older people.

Table 4. **Predictors of viral load <400 copies/mL at month 3**

	Odds ratio	*95% confidence interval*	*P*
Infection with resistant vs wild-type virus	0.26	0.11 to 0.65	<0.01
Higher baseline viral load (per 1-log increment)	0.52	0.4 to 0.78	<0.01
Age at enrollment (per 10-year increment)	1.30	0.92 to 1.82	0.13

Multivariate analysis adjusted for age, gender, baseline viral load and CD4 count, and time since HIV infection.
Source: Marie-Laure Chaix, abstract 114.

Why did so many people infected with resistant virus start treatment with mutant-menaced drugs? Because no one had their virus genotyped before therapy began. A second study by Chaix rated empiric first-line therapy especially risky in people infected with MDR virus [abstract 122]. But three of five people who started treatment without the benefit of genotyping did just fine despite being saddled with multiresistant virus. And two other people infected with pan-resistant virus maintained a stable disease course for two years despite foregoing therapy.

This analysis started with 797 people infected with HIV since 1996. Ten of them (1.25%) cached virus resistant to at least one drug in the first three classes of antiretrovirals. Among five people who began treatment without resistance testing, Chaix retrospectively found that three had virus resistant to two drugs and two had triple-class resistance.

These five people had a sluggish median one-year CD4 gain of 33 cells/mm^3. But three of them pushed their viral load below 50 copies/mL within six months and maintained that response through a median 36 months of follow-up. The other two, however, still had a viral load above 1,000 copies/mL after one and three years of follow-up. Chaix did not distinguish responders from nonresponders on the basis of active drugs in their starting regimen.

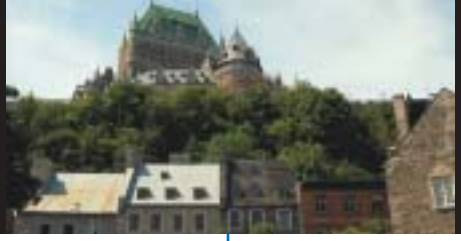
Among the other MDR people not lost to follow-up, two did not start therapy. Their CD4 counts stayed above 500 cells/mm^3 for two years. Then one count sank to 268 cells/mm^3 after 30 months of infection.

Resistance persistence in semen

Transmitted resistance-conferring mutations persist in plasma for years.[13-15] They may last even longer in semen, where resistance really matters for people picking up HIV during sex with a man.

That conclusion rests on a study of five gay men by Davey Smith (University of California, San Diego), who edified workshop attendees with the estimate that 16,000 gallons of HIV-laden semen (60,000 liters) get spilled daily [abstract 115]. Smith also figured that 8,000 people will get inseminated with HIV today. To reckon consequences of this Rabelaisian incidence, he tracked mutant virus in semen of five men who got NNRTI-linked mutations when infected by other men.

Using population sequencing—not a supersensitive resistance assay—Smith recorded mutations in semen of one man up to 1,179 days after the estimated date of HIV infection—even though virus in blood samples proved sensitive to NNRTIs at that point. Drug-susceptible virus did not turn up in semen of another man until an estimated 1,193 days after infection. The other three men still have NNRTI resistance mutations in semen. Resistant virus, Smith concluded, can last over three years in semen and apparently sticks around in semen even longer than in blood.



RESISTANCE AND OUTCOME

Everyone knows resistant virus is a bad thing to have, and triple-class-resistant virus is even worse. But the risk attending treble resistance may have seemed less imminent before the presentation of UK data by the Health Protection Agency's Deenan Pillay. Work from Andrea De Luca (Catholic University, Rome), meanwhile, linked a solitary protease mutation to a higher risk of disease progression. And ACTG researchers confirmed—once again—that resistant HIV can emerge when people with undetectable virus take a drug break.

Infection with multidrug-resistant virus meant an 8% death rate within two years, a big UK survey found. In a single-center Italian study, resistance to NNRTIs boosted the risk of progression almost as much as multiclass resistance.

MDR, GSS, life, and death

A large survey of Britons with MDR virus found that nearly one in 10 died within two years of their MDR diagnosis [abstract 5]. Pillay marshaled data from this copious cohort to suggest that resistance testing and smart regimen swapping—rather than riding the same failing regimen—improve survival chances.

Pillay's analysis rests on the UK HIV Drug Resistance Database, set up in 2001 to bank resistance test results from clinical practice. This stockpile now brims with over 15,000 test results covering about 85% of antiretroviral-treated people in Britain. Pillay defined MDR virus as HIV spotted with mutations from the first three antiretroviral classes. He toted a genotypic sensitivity score (GSS) by adding

- 1 if all resistance reports saw the virus as sensitive to a drug
- 0.5 if reports registered "intermediate" resistance to that drug
- 0 if any report labeled the virus resistant

So a higher GSS is better.

When the 628 people studied learned they had MDR HIV, they had a median CD4 count of 238 cells/mm^3 (IQR 110 to 376 cells/mm^3) and a median viral load of 4.2 log copies/mL (about 15,850 copies/mL, IQR 3.5 to 4.8 log). They had tried a median of eight antiretrovirals (IQR two to 14) and had spent a median of 4.5 years on therapy (IQR 3.1 to 6.8).

Pillay recorded 54 deaths after MDR diagnosis in a median follow-up of 24 months. Estimated probability of death measured 3% one year after MDR diagnosis, 8% two years after, and 13% three years after.

Regression analysis to thresh out survival predictors involved 321 people with at least six months of follow-up after they learned their MDR status. To no one's surprise, a higher CD4 count at that point ($P = 0.013$), a lower viral load ($P = 0.006$), more recent year ($P = 0.024$), and lower number of drugs tried ($P = 0.002$) improved the odds of survival. Years of treatment, GSS of the original regimen, number of active drugs in the original regimen, change in number of inactive drugs, and boosted PI therapy did not independently influence survival.

This analysis also uncovered a trend ($P = 0.143$) toward prolonged survival in people who switched regimens after their MDR verdict came in. Compared with people who continued the same regimen with MDR virus, two groups had a better shot at longer survival:

- Those who changed therapy and maintained the same GSS (relative risk [RR] 0.35, 95% CI 0.16 to 0.80)
- Those who changed therapy and scored a higher GSS (RR 0.31, 95% CI 0.11 to 0.89)

In contrast, people who switched antiretrovirals but ended up with a lower GSS had about a 50% higher risk of death than those who stuck with the same regimen (RR 1.49, 95% CI 0.17 to 13.0). Everyone knows that changing drugs won't slow HIV if the new regimen doesn't work. This analysis suggests that changing drugs and picking up new mutations curtails survival. On the other hand shifting to different drugs and improving the GSS made longer life more likely—and hiking the GSS by a single point correlated with a higher CD4 count 24 weeks after the change.

Pillay believes his results "support an active management strategy of patients diagnosed with MDR HIV-1, including resistance test-guided optimization of therapy." But the results also suggest that *misguided* tries at improving a failing regimen may imperil a person's lease on life. With the resistance data quagmire growing more glutinous daily, clinicians need expert help more than ever.

Progression with one protease mutation

De Luca analyzed the impact of resistance on disease progression at a single institution [abstract 32], but this quiz involved more people, 601, than the British regression analysis just reviewed. He tracked clinical progression in adults who had a resistance test to guide treatment from 1998 through 2004, and follow-up stretched 2,000 days after the resistance assay.

The cohort had a median baseline CD4 count of 300 cells/mm^3 (IQR 146 to 389 cells/mm^3) and a median RNA of 3.8 log copies/mL (about 6,300 copies/mL, IQR 3.78 to 4.70 log). Most of the study group, 86%, had at least one NRTI mutation, 52% had one or more PI mutations, and 43% had at least one NNRTI mutation. While 23% had single-class

resistance, 42% had virus resistant to two classes and 23% to three classes. Among people with protease mutations, 77% had at least one "universal" protease mutation at position 33, 82, 84, or 90; 23% had two such mutations and 18% three. Two thirds of the cohort carried TAMs.

Eighty people had an AIDS diagnosis or died during 715 person-years of follow-up. Compared with people who had no mutations or mutations conferring resistance to one or two classes, those with triple-class mutations had a 62% higher risk of progression in an analysis adjusted for CD4 count and viral load at genotyping and for prior AIDS diagnosis (95% CI 0.98 to 2.70, $P = 0.013$). In the same type of analysis, people marked with three or more "universal" protease mutations had a 3.43 higher risk of progression (95% CI 1.61 to 7.29, $P = 0.0007$) than people with two or fewer of these mutations.

By itself the I84V protease mutation heightened the risk of progression 1.71 times, though that correlation fell shy of statistical significance in a univariate analysis (Table 5). Every additional TAM raised the risk of progression 1.13 times. And resistance to NNRTIs fostered progression almost as much as triple-class resistance.

Six of 36 people with no PBMC evidence of resistance mutations before taking a structured drug break had mutations in their rebound plasma, as did five of five with PBMC mutations before the drug holiday.

Table 5. **Progression predictors in 601 resistance-tested people***

	Hazard ratio	*95% confidence interval*	*P*
Prior AIDS diagnosis	2.57	1.65 to 4.00	<0.01
Each extra 100 CD4 cells/mm^3	0.82	0.68 to 0.97	<0.01
Each extra log viral load	1.70	1.38 to 2.11	<0.01
NNRTI resistance	1.61	1.04 to 2.51	0.03
NRTI + NNRTI resistance	1.65	1.06 to 2.56	0.02
Triple-class resistance	1.78	1.12 to 2.83	0.01
Three or more "universal" protease mutations	3.33	1.59 to 6.94	<0.01
I84V protease mutation	1.71	0.90 to 2.94	0.09
Each additional TAM	1.13	0.99 to 1.29	0.07

*Univariate analysis based on 715 person-years of follow-up.
Source: Andrea De Luca, abstract 32.

Fast resistance during STI rebound

More than one quarter of people who interrupted an effective regimen had evidence of resistance mutations in plasma within weeks of stopping their drugs, reported Mark Winters (Stanford University, Stanford, California) [abstract 35]. Housing mutant virus in PBMCs before the structured treatment interruption (STI) upped the odds of emergent resistance during the STI, but mutants arose even in some people with previously clean PBMCs.

Winters and ACTG colleagues monitored mutations in 46 people enrolled in study A5102, which randomized participants to add interleukin 2 to their antiretrovirals 16 weeks before the STI or to continue only antiretroviral therapy before the STI. Everyone had a viral load below 200 copies/mL and a CD4 count above 500 cells/mm^3 when they enrolled, and the median time on potent therapy measured 48 months.

All study participants rebounded above 500 copies/mL within eight weeks of stopping therapy. Eleven of 41 people with pre-STI PBMC results (27%) had a resistance mutation in their rebound plasma sample. Eight of 17 (47%) suspending a PI regimen and three of 20 (15%) mothballing an NNRTI had mutants at rebound. People with faster CD4 slippage when they stopped treatment proved significantly more likely to have resistance mutations upon rebound ($P = 0.0004$).

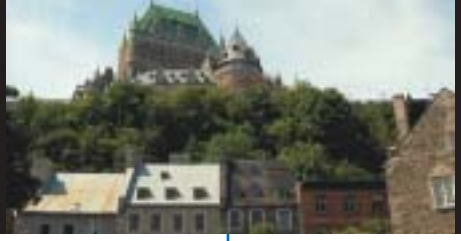
Ten of 11 people with rebound resistance had detectable viremia only two weeks after stopping treatment. The ACTG crew advised monitoring viral load and genotype two weeks into an STI to judge whether it's safe to continue.

All five people with mutations in PBMCs before the STI had mutations in their breakthrough sample, compared with six of 36 people without PBMC mutations before the STI ($P = 0.0006$). Still, the high resistance rate—17%—in people with no evidence of archived mutations before their STI underlines the risks of this strategy.

How adherence affects resistance rates

Wobbly adherence probably poses the greatest threat of resistance. But how much adherence must falter before resistant virus emerges—and how shaky adherence affects specific drugs—remained largely unaddressed until Richard Harrigan and colleagues (University of British Columbia, Vancouver) tackled the issue earlier this year.[16] They found that people with pretty-good-but-not-perfect adherence—80% to 90% measured by prescription refill and untimed drug levels—ran a significantly higher resistance risk than people with utterly awful (<20%) or near-perfect (≥95%) adherence.

At the Resistance Workshop, Harrigan extended this analysis to chart the impact of adherence on specific mutations. The study involved people starting their first antiretrovirals from August 1996 through September 1999. The British Columbia team genotyped 2,805 samples from 1,191 people whose viral load topped 1,000 copies/mL in the first 30 months of treatment. During that span one mutation



arose in 298 people, two in 158, three in 83, four in 42, and three in 28. Whereas 885 people had begun a PI regimen, 306 started with an NNRTI.

Harrigan and colleagues rated adherence by two measures—prescription refills in British Columbia's universal antiretroviral coverage program, and PI or NNRTI levels in the first two blood samples during treatment. A multivariate model adjusting for resistance to each class as a time-dependent variable traced a strong correlation between adherence and resistance to NNRTIs or 3TC, but not to other NRTIs or to PIs.

Compared with 95% or better adherence, 80% to 95% refill-based adherence raised the risk of NNRTI mutations six times (95% CI 3.3 to 10.9, $P < 0.0001$) and of 3TC mutations three times (95% CI 1.9 to 4.7, $P < 0.0001$). When Harrigan figured adherence by refill and drug levels, less than 95% adherence raised the risk of NNRTI mutations seven times (95% CI 3.4 to 14.5, $P = 0.0001$) and of 3TC mutations 4.5 times (95% CI 2.6 to 7.9, $P = 0.0001$). If people refilled prescriptions more than 95% of the time but had low PI or NNRTI concentrations, they had a high risk of mutations involving any drug class.

An everyday drug—valproic acid—helps drain HIV from resting CD4 cells. That may not revive eradication hopes. But another study suggests the strategy could tighten the tap on virus that feeds potentially dangerous blips in viremia.

Can HIV be eradicated?

Many have stopped asking that question, and most stopped doing studies to answer it. But not David Margolis (University of Texas Southwestern Medical Center, Dallas). At last year's Resistance Workshop, he unveiled *ex vivo* experiments showing that reasonable doses of a commonly used drug—the anticonvulsant/antidepressant valproic acid—stymie outgrowth of HIV from resting CD4 cells sampled from aviremic people.[17] At this year's workshop he offered evidence that valproic acid sweeps HIV from T cells still resting *inside* those aviremic people [abstract 148].

Margolis thinks valproic acid rousts HIV from sleepy CD4s by inhibiting histone deacetylase (HDAC). Stifling HDAC perks up HIV promoter and viral expression without waking up every T cell in town. He tested that theory in a pilot trial involving four people who kept their viral load below 50 copies/mL for an average 46 months with antiretroviral therapy.

As a protective measure Margolis first added the fusion inhibitor ENF to each person's regimen for four to six weeks to bar HIV from uninfected cells during valproic acid therapy. Then study participants took valproic acid for another three months, maintaining drug levels from 50 to 100 µg/mL with weight-based doses around 500 to 750 mg twice daily.

Three of four volunteers had significant drops in resting T cells housing replication-competent HIV. The downturns averaged 64% and ranged from 52% to more than 84%. Falls in infectious units per million cells ranged from 29% ($P = 0.035$) to more than 84% ($P < 0.009$). Antiretroviral therapy alone doesn't do that. Everyone tolerated valproic acid well. Margolis plans to continue studying the drug, but next without the ENF shield.

Study results appeared in *Lancet* shortly after the workshop.[18] There, Margolis allowed himself a conclusion bolder than any heard since 1996: "This finding, though not definitive, suggests that new approaches will allow the cure of HIV in the future."

Draining the last drop of infectious virus from T-cell reservoirs will not eradicate HIV. The virus has too many hiding places. But siphoning some HIV from resting cell reservoirs could pay other dividends. At least that's what one might conclude from recent work at the University of Washington.[19]

Studying 37 children with well-controlled viral replication, the University of Washington's Lisa Frenkel and coworkers took a stab at that enduring question—where does blip virus come from: archived HIV or creeping replication? Frenkel's evidence suggested that *both* sources may fuel viral spikes during apparently suppressive therapy. And those spikes, she confirmed, are not innocuous. Resistance mutations evolved in virus of one child with frequent blips.

Will tightening the reservoir tap—with valproic acid or some other agent—stop inevitable resistance drips? No one knows. That's why the import of studies like these should not be minimized.

The Wallace Stevens line quoted at the top of this article ends, by the way, thus:

> *…And yet relation appears,*
> *A small relation expanding like the shade*
> *Of a cloud on sand, a shape on the side of a hill.* ■

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

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AIDS

Cumulative exposure to nucleoside analogue reverse transcriptase inhibitors is associated with insulin resistance markers in the Multicenter AIDS Cohort Study

Brown TT, Li X, Cole SR, et al.

OBJECTIVE: To estimate insulin resistance and its relationship to antiretroviral therapy (ART) in a cohort of HIV-infected persons with comparison to HIV-seronegative controls. *DESIGN:* Prospective cohort of 533 HIV-infected and 755 HIV-seronegative men in the Multicenter AIDS Cohort Study evaluated at six-month intervals between 1999 and 2003. *METHODS:* Recent ART exposure was assessed by type of treatment in the preceding six months (ie, no ART, monotherapy, combination ART, or highly active antiretroviral therapy [HAART] with and without a protease inhibitor [PI]). Cumulative exposure was determined for the three major ART classes and for individual medications within each class. Two endpoints, a modified QUICKI index, 100 x $1/(\log^{10}[\text{glucose}] + \log^{10}[\text{insulin}])$ and fasting hyperinsulinemia (insulin >15 [µ]U/ml), were assessed. All statistical models were adjusted for age, body mass index, race, nadir CD4 cell count, hepatitis C serostatus and family history of diabetes mellitus. *RESULTS:* Each of the HIV-infected groups had higher odds of hyperinsulinemia and lower mean QUICKI than the HIV-seronegative men. Each additional year of exposure to nucleoside analogue reverse transcriptase inhibitors (NRTI) was associated with increased odds of hyperinsulinemia (odds ratio [OR], 1.08; 95% confidence interval [CI] 1.02-1.13) and a lower QUICKI (-0.04; 95% CI, -0.07 to -0.01). Cumulative exposure to nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs) or PI drugs was not associated with either insulin resistance marker. Of individual medications examined, stavudine was associated with the highest risk of hyperinsulinemia (OR, 1.2; 95% CI, 1.2-1.3). *CONCLUSIONS:* Fasting surrogate markers suggest increased insulin resistance in HIV-infected men, which is related to cumulative NRTI exposure.

AIDS. 2005;19(13):1375-1383.

Sexually Transmitted Infections

Increasing detection of asymptomatic syphilis in HIV patients

Cohen CE, Winston A, Asboe D, et al.

BACKGROUND/OBJECTIVES: The burden of new syphilis diagnoses in London has mainly been in men who have sex with men (MSM), many of whom are coinfected with HIV. Our HIV unit introduced regular serological screening for syphilis during routine follow-up care to detect patients who may be at risk of asymptomatic infection. We assessed if this remained an effective and necessary strategy in the second year since introduction. *METHODS:* All HIV outpatients with newly positive syphilis serology between May 1, 2002, and April 30, 2003, were identified using a prospectively collected database. Only patients who were asymptomatic at the time of screening were included (cohort B). They were compared to patients in the exact preceding year (cohort A). *RESULTS:* 2,655 patients had at least one CD4 count measured in the period (surrogate marker for patients having routine follow-up bloods), of whom 2,389 (90%) had syphilis serology performed. Forty individuals were found to have early asymptomatic infection (two were re-infections), compared to 26 patients in cohort A. These 40 patients represented 36% of all patients with infectious syphilis treated within our department, and 56% of those who were HIV-positive. The event rate in cohort B was 7.3 per 1,000 patient years (confidence interval [CI] 5.2 to 9.9) compared to 2.8 (CI 1.8 to 4.0) in cohort A. *CONCLUSION:* Routine screening is effective and has detected increasing numbers of HIV outpatients with early asymptomatic syphilis. Our department will continue this strategy for all HIV patients during their follow-up care. We recommend that other units adopt similar initiatives that assist with regional control of the UK syphilis epidemic.

Sex Transm Infect. 2005;81:217-219.

Clinical Infectious Diseases

Risk factors for and outcome of hyperlactatemia in HIV-infected persons: Is there a need for routine lactate monitoring?

Imhof A, Ledergerber B, Gunthard HF, for the Swiss HIV Cohort Study

BACKGROUND: Lactic acidosis is a rare but life-threatening complication of combination antiretroviral therapy (CART). Asymptomatic or mildly symptomatic episodes of hyperlactatemia are more frequent, but their clinical relevance is unknown. *METHODS:* The incidences of, risk factors for, and courses of hyperlactatemia and lactic acidosis were prospectively assessed in the following three groups at the Zurich center of the Swiss HIV Cohort Study: persons already receiving CART at baseline, treatment-naive persons who initiated CART during the observation period, and persons who received no CART before or during the observation period. *RESULTS:* During 4,788 person-years of follow-up, a total of 22,678 lactate assessments were performed for 1,566 persons; 662 (42.3%) had at least one lactate level measurement of >2.4 mmol/L, and 49 (3.1%) had severe hyperlactatemia (lactate level of >5.0 mmol/L). The incidence of hyperlactatemia was 227 cases (95% confidence interval [CI], 210-245) and 59 cases (95% CI, 38-93) per 1,000 person-years of follow-up among persons with and persons without CART, respectively. During the observation period, the incidence decreased from 459 cases (95% CI, 415-508) to 85 cases (95% CI, 76-107) per 1,000 person-years of follow-up, respectively, because of changing CART prescription patterns. Severe hyperlactatemia occurred in treated persons only. In multivariable Cox proportional hazards models, significant risk factors for severe hyperlactatemia were regimens containing stavudine and didanosine (hazard ratio [HR], 6.65; 95% CI, 2.70-16.3) and regimens containing efavirenz (HR, 2.85; 95% CI, 1.31-6.21). Lactic acidosis was diagnosed in four of 1,566 persons, all of whom were receiving stavudine and didanosine. *CONCLUSIONS:* Hyperlactatemia was frequently observed in all three groups, but severe hyperlactatemia and lactic acidosis were rarely observed among persons who received CART. Lactate monitoring appears to be indicated primarily for persons receiving stavudine and didanosine and for persons who are symptomatic. Long-term follow-up is needed to investigate the risk of novel treatment regimens for hyperlactatemia.

Clin Infect Dis. 2005;41(5):721-728.

Journal of Infectious Diseases

Influence of hepatitis C virus infection on HIV-1 disease progression and response to highly active antiretroviral therapy

Rockstroh JK, Mocroft A, Soriano V, et al. for the EuroSIDA Study Group

OBJECTIVE: To assess hepatitis C virus (HCV) antibody prevalence in the EuroSIDA cohort, along with survival, human immunodeficiency virus (HIV)-1 disease progression, virologic response (plasma HIV-1 RNA load of <500 copies/mL), and CD4 cell count recovery by HCV serostatus in patients initiating highly active antiretroviral therapy (HAART). *RESULTS:* HCV serostatus at or before enrollment was available for 5,957 patients; 1,960 (33%) and 3,997 (67%) were HCV-seropositive and -seronegative, respectively. No association between an increased incidence of acquired immunodeficiency syndrome-defining illnesses or death and HCV serostatus was seen after adjustment for other prognostic risk factors known at baseline (adjusted incidence rate ratio [IRR], 0.97 [95% confidence interval {CI}, 0.81-1.16]). However, there was a large increase in the incidence of liver disease-related deaths in HCV-seropositive patients in adjusted models (IRR, 11.71 [95% CI, 6.42-21.34]). Among 2,260 patients of known HCV serostatus initiating HAART, after adjustment, there was no significant difference between HCV-seropositive and -seronegative patients with respect to virologic response (relative hazard [RH], 1.13 [95% CI, 0.84-1.51]) and immunologic response, whether measured as a ≥50% increase (RH, 0.94 [95% CI, 0.77-1.16]) or a ≥50 cells/µL increase (RH, 0.92 [95% CI, 0.77-1.11]) in CD4 cell count after HAART initiation. *CONCLUSIONS:* HCV serostatus did not affect the risk of HIV-1 disease progression, but the risk of liver disease-related deaths was markedly increased in HCV-seropositive patients. The overall virologic and immunologic responses to HAART were not affected by HCV serostatus.

J Infect Dis. 2005;192(6):992-1002.

HIV/HCV coinfection and progression to AIDS

Michael Carter

HIV-positive patients who are coinfected with hepatitis C virus (HCV) are significantly more likely to develop an AIDS-defining illness or experience a drop in their CD4 cell count to below 200 cells/mm^3 than patients who are only infected with HIV, according to data from London's Chelsea and Westminster Hospital, published in the September 15, 2005, edition of *Clinical Infectious Diseases*.

The study, involving every patient who attended the Chelsea and Westminster Hospital since antiretroviral therapy (ART) became available and who underwent testing for HCV, found that although the rate of CD4 count decline did not differ significantly between coinfected patients and those who were HIV-monoinfected, patients who were coinfected with HCV were significantly more likely to progress to AIDS.

Although there is good evidence that HIV can worsen the course of HCV-related disease, there are conflicting data concerning the impact of HCV on HIV. Since the advent of ART, liver disease caused by HCV has emerged as a significant cause of illness and death in HIV-positive patients. Investigators from the Chelsea and Westminster Hospital therefore wished to compare rates of disease progression between HIV/HCV-coinfected patients and those who were HIV-monoinfected.

The endpoints for the study were the onset of an AIDS-defining illness or a fall in CD4 count to below 200 cells/mm^3. All patients presenting at the hospital since January 1996 with a CD4 count above 200 cells/mm^3 were included in the study.

A total of 5,800 patients were treated at the Chelsea and Westminster Hospital since ART became available. Of these, 2,000 met inclusion criteria for the study and fewer than 1,500 of these individuals were tested for HCV. A total of 85 patients tested positive, providing a coinfection rate of less than 6%.

Patients who were ART-naive were significantly less likely to experience an event than patients taking ART. This was because they had higher CD4 counts. Women were more likely than men to progress to AIDS or a CD4 count below 200 cells/mm^3 ($P = 0.034$), and there was a 1% increase in risk for each one-year increase in age.

In multivariate analysis, the investigators found that patients who were HIV/HCV-coinfected were 52% more likely to progress to AIDS or a CD4 count below 200 cells/mm^3. However, the rate of CD4 count decline was similar between HIV-infected patients and patients coinfected with HIV and HCV.

According to the investigators, "although analyses did not show any differences in CD4 count decreases between HIV-1-infected patients and patients with HIV-1/HCV coinfection, the groups differed with respect to the likelihood of having an event." This suggested to them "that HCV infection is having an effect on HIV-1 disease progression that is not reflected in CD4 count." The investigators suggest that this could be because HCV was having an effect on CD8 cytotoxic T cells or dendritic cells. ■

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Adebisi MA Lawal

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

This month, *IAPAC Monthly* is proud to feature Adebisi MA Lawal, Chief Medical Officer/Family Physician at the Ngwelezane Hospital in Empangeni, South Africa.

What proverb, colloquial expression, or quote best describes how you view the world and yourself in it?
Live and let's live.

What activities, avocations, or hobbies interest you? Do you have a hidden talent?
Philosophy, metaphysics, reading. My hidden talent is my ability to read a person's "aura."

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

Who are your mentors or real life heroes?
Mahatma Gandhi, Nelson Mandela.

With what historical figure do you most identify?
Kwame Nkrumah of Ghana.

Who are your favorite authors, painters, and/or composers?
Composer: Beethoven. Painter: Michelangelo.

If you could have chosen to live during any time period in human history, which would it be?
Now. It is an exciting time for scientific discovery.

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

In your opinion, what are the greatest achievements and failures of humanity?
Achievements: Technological advancement. Failures: The conflict of man against man throughout humanity, and an inability to learn from history.

What is your prediction as to the future of our planet one full decade from present day?
There would be a cure for AIDS!! ■

SAY ANYTHING

The key to an adequate AIDS response in China lies in three changes: from policy to action, from pilots to scaling-up program implementation, and from health response to societal involvement.

Zhao Pengfei, Program Officer with the China Office of the World Health Organization (WHO), in an August 16, 2005, Xinhua News Agency report about that country's AIDS epidemic. China is increasing its focus on commercial sex work, as sexual activity has become the most common method of HIV transmission in China, and as this activity has expanded HIV infection from high-risk groups into the mainstream population. China has rolled out its "100% condom use programs," with their slogan of "No Condom, No Sex," in several provinces, and is planning to expand this program in an attempt to make condoms available at more locations where commercial sex takes place.

The Global Fund has decided to suspend its five grants to Uganda because there is evidence of serious mismanagement by the Project Management Unit.

An excerpt from an announcement issued by the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) as quoted in an August 24, 2005, Reuters report entitled, "Fund Halts AIDS Cash to Uganda over Mismanagement." According to the Reuters report, the Global Fund said its auditors have raised serious questions about the operations of the special agency created by the Ugandan government to administer the Global Fund's cash allocations. The announcement cited "inappropriate expenditure and improper accounting" but no clear indication of fraud or corruption. The suspension is to last two months, during which time Uganda is to implement a new system for handling Global Fund money. The Global Fund earmarked US$201 million for Uganda during a two-year period. To date the country has received approximately US$45 million.

Yes, it is.

Lee Jong-wook, Director-General of the World Health Organization (WHO), in an August 23, 2005, Reuters report about an emergency meeting of African health ministers in Maputo during which they declared tuberculosis (TB) a public health emergency. According to the WHO, the number of TB cases has quadrupled in 18 African countries in the past 15 years. In addition to agreeing with their characterization of the TB crisis in Africa, Lee echoed the ministers' call for greater access to antiretroviral drugs.

Although I don't use it, I know what it is.

Quote from a Taiwanese safer sex poster, as cited in an August 24, 2005, Deutsche Presse-Agentur report. The poster, which featured a Catholic nun holding a condom, had been displayed in Taipei's subway stations. The poster drew strong criticism from Taiwan's Catholic population, forcing the Taipei United Hospital to remove all copies within a one-week timeframe.

Of the 75 clients we have, there are about 50 who are on the waiting list to be added to ADAP [AIDS Drug Assistance Program].

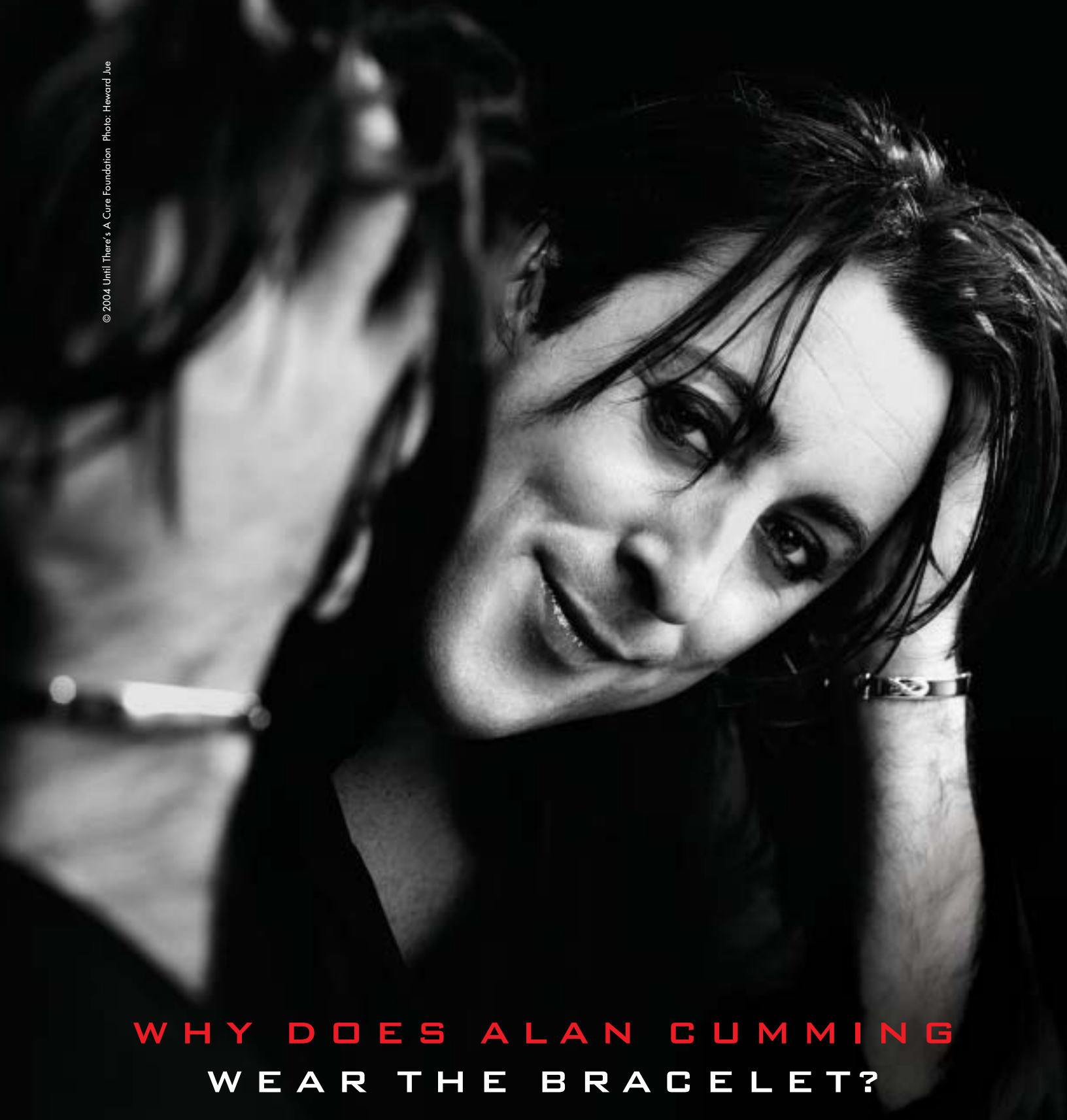
Zita Roberts, an HIV/AIDS case manager for the Cleveland County Health Department, in an August 9, 2005, Shelby Star *article about HIV/AIDS care and treatment for low-income, HIV-positive patients in the Cleveland County area.*

I hope this doesn't just end today.

Sandra Trotter, an adult student at Wichita State University, quoted in an August 21, 2005, Wichita Eagle *article covering a gathering of 60 people there to strategize around fighting AIDS among African Americans. According to those gathered for the meeting, the AIDS epidemic's disproportionate impact on African Americans makes openness about the topic all the more important. The Kansas Department of Health and Education reports that African Americans, who make up just 6% of the population, accounted for 26% of AIDS diagnoses between 2000 and 2002. Participants plan to organize and create culturally specific HIV prevention and intervention resources for various age groups.*

Without prejudice to our understanding of the international rules of the game, what comes first are the interests of the citizens of each country.

Gines Gonzalez Garcia, Argentina's Minister of Health and Environment, in an August 25, 2005, Chicago Tribune *article about his country's pact with Brazil to work together in producing generic antiretroviral drugs. While providing little information about the agreement, including how soon production might begin, the two countries will start by sharing information and technology and by bringing experts together.*



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