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IAPAC



MONTHLY



MAKING
RIGHT TURNS
IN THE HIV
PHARMACOLOGY
MAZE

232



Making right turns in the HIV pharmacology maze

Mark Mascolini

The roads to the “Eternal City” may be straight and simple, but the roads in Rome are a maze. Researchers at the 5th International Workshop on Clinical Pharmacology of HIV Therapy in Rome showed that HIV pharmacology can seem straight and simple too. But as soon as that research moves from the straight-and-narrow effects of drug interactions—and sometimes even sooner—parsing results can get as perilous as plotting your course from the Palazzo Farnese to the Campidoglio.

DEPARTMENTS

REPORT FROM THE PRESIDENT	226
PUBLIC POLICY	228
ABSTRACTS	258
FOCUS ON HEPATITIS	260
IN THE LIFE	262
SAY ANYTHING	263



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

One world, multiple standards

José M. Zuniga

In July 2000, the global AIDS community gathered at the XIII International AIDS Conference in Durban, South Africa, to “*break the silence*” and bolster action to stem the devastating impact of HIV and AIDS in the developing world. Four years after this clarion call to mobilize both the political will and resources necessary to expand access to antiretroviral drugs, and to overcome social and political barriers to health and human development for all, we are called upon to ask: *How far have we come?*

As we gaze back upon the landscape over which we have journeyed since 2000, do we see mountains and gulfs that have been surmounted, or rather a gentle ripple of hills that were but the prelude to greater, forthcoming obstacles? While respect is due the various achievements that have been realized since 2000 in expanding access to care and treatment, I would argue that ultimate judgment about our progress in this respect will only truly be possible by evaluating what is occurring at the point of care for patients—that point of intersection where the rhetoric of commitment meets (or does not) the beds, food, syringes, drugs, and care providers that collectively help to determine the fate of those who seek access to them. And so, where we have succeeded in focusing global attention on the AIDS pandemic and now prepare to gather in Bangkok this month for the XV International AIDS Conference to plan next steps and organize efforts aimed at ensuring that AIDS remains key among competing global priorities, it is my sincere hope that equal attention will be placed on continuing needs at the point of healthcare delivery, where the “rubber meets the road,” as the saying goes.

It is a great understatement to say healthcare delivery in our world varies immensely in quality and availability. But we must address the nascent, ethical questions couched in that statement: Are we willing to accept multiple standards? If not, what does that imply, and subsequently, what does that then further require of us? It is revealing of our ambivalence on this matter that in the very calculus of our international public health efforts (HIV being no exception) we accept as a general precept and variable the very impoverishment of care capacity and the absence of important infrastructure in determining many of our responses and interventions. A common clinical rejoinder to this approach, as has been memorialized in ongoing debate between population *versus* individual health, is that by accepting these limitations and standards in order to provide some care for *all* and maximum benefit at the society level, individual health outcomes are very often sacrificed. It is a frustrating toss-up that is perhaps nowhere better exemplified today than through the lens of the global AIDS pandemic.

Where questions of what is required to optimize individual care in resource-constrained settings seem so often to rub uneasily against the imperatives of caring for masses of HIV-positive people, preventing further spread of disease, and accomplishing this feat within the narrow bounds of existing capacity, we face difficult choices. And so, while the progress that we have achieved in dealing with the pandemic bespeaks the fact that more and more of us seem to be appreciating that we are our brother’s keeper—as the spiritual saying goes—just how well we are keeping him is the question around which I feel we owe greater attention.

As we reach the mid-point of 2004, the lion’s share of our collective energy is currently dedicated to expanding access to antiretroviral therapy so desperately needed in most places of the world—and rightly so. At the same time, however, we must ask ourselves whether we are being equally thoughtful with respect to accompanying care concerns, examining from both clinical and ethical perspectives what patients *deserve*—be they in New York or New Delhi—and in many cases *must have*, in accessing this life-saving and -enhancing treatment, and maximizing its benefit. Many challenging questions stand before us, and I fear that as we proceed with due haste to expand our treatment efforts in resource-constrained settings we risk allowing the ultimate consideration of patient outcomes and quality of life to be greatly overshadowed by competing arguments for cost containment, rapid response, and social benefit.

While certain of these issues have been raised in objection to our desire to expand access to antiretroviral therapy—the “developing world is not ready for antiretroviral therapy” argument (which is, incidentally, a view not shared by the International Association of Physicians in AIDS Care [IAPAC])—I would agree that the singular merit of this argument is that, *yes, indeed*, effective delivery of antiretroviral therapy will be a great challenge should healthcare capacity remain as it is in many places. However, rather than accept this state of affairs, as detractors from the antiretroviral therapy expansion movement may do, we are compelled instead to turn this question back upon ourselves and ask how it is that we allow these impoverished conditions to exist. When we adapt our responses too much to fit existing treatment capacity, without working to improve that capacity

and the underlying poverty that holds it back, our responses risk being unsustainable or ill conceived. What we are now learning about the use of single-dose nevirapine (NVP) for prevention of mother-to-child transmission of HIV stands as an example.

In raising these points, I contend that the best immediate prescription for this dilemma is increased attention to its persistence. My ultimate concern is that unless we submit these questions to debate, we risk losing sight of the single common denominator that must unite us and guide our various actions as we look to the future: an improvement in the healthcare standards, capacity, and tools necessary to ensure the optimal care of patients, regardless of where they live. I deliberately say “patients” here, not “HIV patients,” recognizing that as we expand access to treatment for HIV disease we also risk pitting it against other diseases in our effort to secure and spend scarce resources. This, too, is an imminent danger that we must avoid.

While immediate, *ad hoc* solutions and interventions may be the tough pill that we must swallow in order to get us further on down the road, I would like to argue that we must accept as a terminal point no less than a single, equal standard of care and treatment for all people living with HIV/AIDS. It is with a view to contributing to global dialogue around this issue of concern that on July 15, 2004, IAPAC will be hosting an official satellite symposium of the XV International AIDS Conference that will be dedicated to examining the global state of AIDS care in 2004. Through this critical opportunity, IAPAC wishes to increase attention to continuing disparities in care standards globally, to examine their implications, and to address the serious needs of patients and care providers alike in ensuring optimal clinical outcomes and, as important, enhanced quality of life.

In ending this month's Report from the President, I wish to quote from former United Nations Secretary-General Dag Hammarskjöld who, in championing human

rights and international development in a manner unlike many before or since him, reminded us that, “to let oneself be bound by a duty from the moment you see it approaching is part of the integrity that alone justifies responsibility.” If we have answered the difficult question of whether we accept multiple standards of care in the negative, then it follows that we have admitted responsibility for fostering and creating change. Our duty in redressing these multiple standards still lies ahead, and surely our integrity hangs in the balance. If I may venture a final personal thought, I would opine that the immediate answer is to insist on asking difficult questions, to not shy away from hard wars in favor of easy battles, and to not let our imaginations and actions be bound by the realities of the present. ■

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



7th International Conference on Healthcare Resource Allocation for HIV/AIDS HIV/AIDS and the United Nations Millennium Development Goals: Are We on Target?

November 3 - 4, 2004 - Washington, DC

Call for Abstracts

At the UN Millennium Summit in September 2000, world leaders placed sustainable development at the heart of the global agenda by adopting eight Millennium Development Goals (MDGs) that set clear targets for reducing poverty, hunger, disease, illiteracy, conflict, environmental degradation, and discrimination against women by 2015.

Goal 6 commits nations to specifically “combat HIV/AIDS, malaria, and other diseases.” The UN Millennium Project—spearheaded by Jeffrey Sachs (Columbia University)—has identified 10 priority areas through which to achieve Goal 6. Four years after the UN Millennium Summit, the 7th International Conference on Healthcare Resource Allocation for HIV/AIDS (7th ICHRA) aims to assess global responses to Goal 6 as well as our relative success in addressing the related 10 priority areas.

The International Association of Physicians in AIDS Care (IAPAC) thus welcomes abstract submissions for the 7th ICHRA along the following 10 tracks (representing the 10 priority areas):

- Track 1 Access to Treatment
- Track 2 Health System Investment to Support HIV/AIDS Services
- Track 3 Prevention of HIV Transmission
- Track 4 HIV/AIDS and Vulnerable Populations
- Track 5 Integration of HIV Prevention, Care, and Treatment Efforts
- Track 6 Empowerment of Women to Combat HIV/AIDS
- Track 7 Strategies to Address HIV/AIDS in Orphans and Vulnerable Populations
- Track 8 Enhancing the United Nations Response
- Track 9 Expanding and Improving Implementation of Domestic and International Funding for HIV/AIDS
- Track 10 Empowerment of Governments and Measures for Accountability

The deadline for electronic abstract submission is August 4, 2004.

Visit www.iapac.org to submit your abstract(s).



Clinical trials without ethical review

Fiona Fleck

A recent series of unethical, and in some cases illegal, clinical trials in India is fuelling concern over the incidence of clinical trials conducted without ethical approval in other countries where legislation may be either inadequate or not implemented.

In a series of articles last year, Chandra Gulhati, Editor of the *Monthly Index of Medical Specialities* (an independent pharmaceuticals journal in India), shed light on the conduct of illegal trials and subsequent promotion of the anti-cancer drug, letrozole, as a fertility drug in India.

More than 400 women, who had been trying in vain to conceive, were enrolled without their knowledge or consent to take part in clinical trials across India to see if the drug induced ovulation. The drug, which was produced by Mumbai-based generics manufacturer, Sun Pharmaceuticals, was a copy of Novartis's patented drug, Femara®. The women were under the impression they were receiving an expensive fertility treatment.

Belonging to a class of drugs known as aromatase inhibitors, letrozole has been approved globally for the treatment of breast cancer in post-menopausal women, but it is not approved for any other use in any country, including India.

Since then, India has seen a huge public outcry over the regulatory authorities' failure to crack down on a recent series of illegal, and legal but unethical, clinical trials.

A New Delhi-based nongovernmental organization is filing a complaint about the letrozole case to India's Supreme Court. And the Indian government has

pledged to push through tougher, more effective legislation to tackle the problem later this year.

Gulhati contends that although the company as well as the physicians who carried out the trials broke the law, no one has been subjected to criminal investigation by the Indian authorities.

The letrozole trials are a shocking example of a widespread global phenomenon. A recent survey of more than 200 health researchers concluded that a quarter of clinical trials conducted in developing countries do not undergo ethical review. The survey, which was commissioned by the former US National Bioethics Advisory Commission, was published in February 2004.

John Williams, Director of the Ethics Section of the World Medical Association (WMA), said drug approval agencies in developed countries, such as the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMA), require ethics committee approval of trials for the sale and distribution of any drug.

"These are strong incentives to seek such approval," Williams said, adding that editors of major journals also require such approval for studies submitted for publication.

"There are efforts under way to strengthen ethical review throughout the world through SIDCER and its regional committees," Williams said, referring to the Strategic Initiative for Developing Capacity in Ethical Review, an international project to develop the ethical review of biomedical research globally.

Most but not all developing countries have ethical review committees in the form of research institutes or other scientific panels. But training must be provided to ensure that these panels are independent

and able to review clinical trials without prejudice.

The letrozole case illustrates this problem well. Gulhati said pharmaceutical companies in India often have a "cozy relationship" with regulators and bribe researchers—hired to conduct purportedly independent clinical trials—with expensive gifts, paid speaking engagements, over-paid consultancy work, and free overseas holidays. He said there was no independent safety monitoring of clinical trials and that participants sometimes do not even know they are participating in tests.

"Neither the regulatory authorities nor the ethics committees seek conflict of interest information from investigators," Gulhati said, adding, "Most of the clinical trials here are conducted without any arrangement for compensation in case of study-related injury, disability, or even death."

These initiatives come at a time when pharmaceutical and biotechnology companies try to save time and money by conducting clinical trials in developing countries, where there are plenty of willing subjects and often more relaxed regulatory mechanisms.

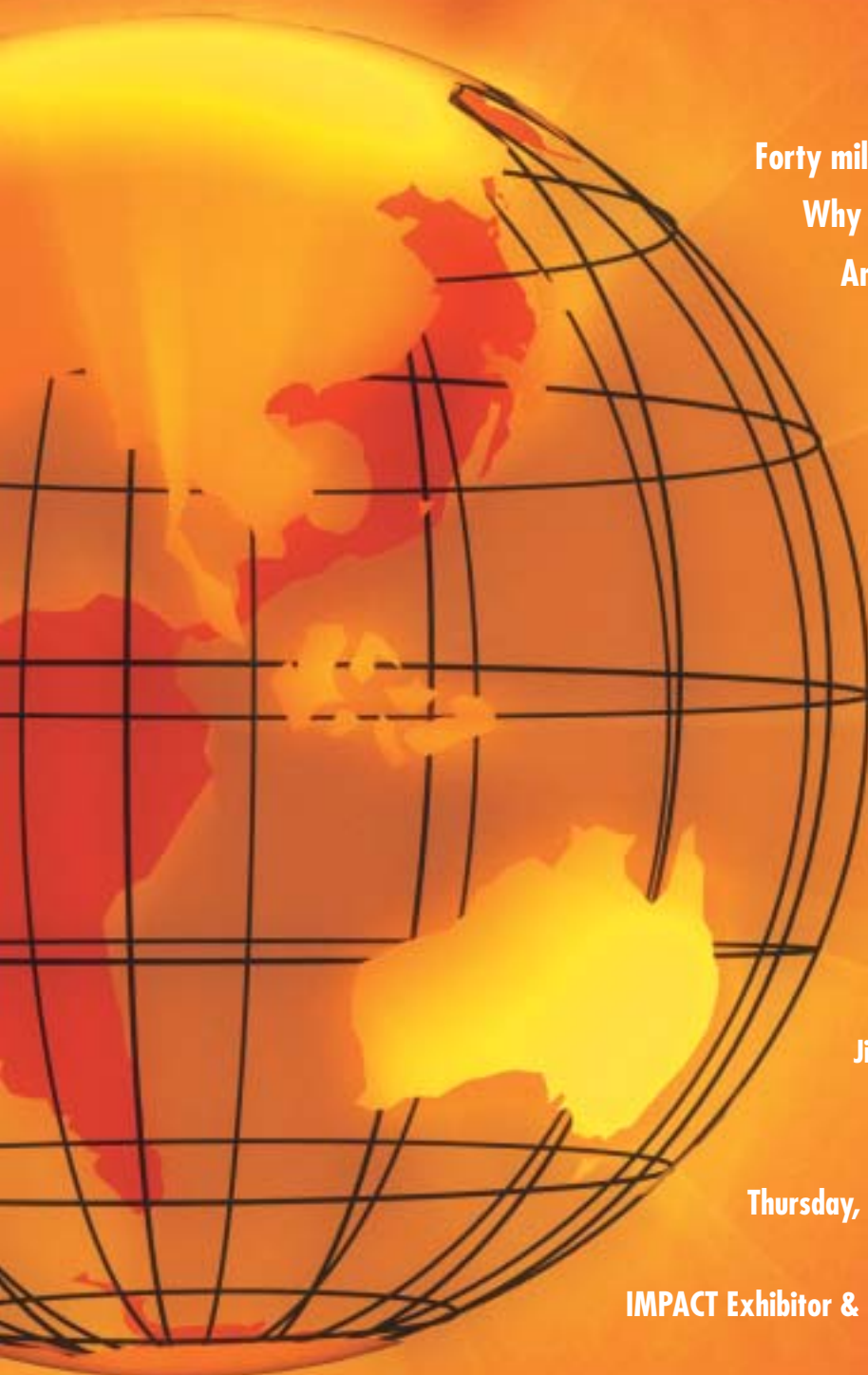
Harvard Medical School's Eugene Braunwald, who chairs a clinical trials group, told the *New York Times* recently that half as many US patients are enrolling in clinical trials compared to five years ago.

The trend of outsourcing clinical trials to developing countries has sparked concerns about unscrupulous biotechnology and pharmaceutical firms exploiting the healthy, who hope to earn some cash, and the sick, who hope to get free treatment.

A key question for regulators is whether US drug manufacturers should apply FDA standards when they conduct trials abroad. This will be less of an issue once developing countries tighten laws and make their ethical review panels truly independent. ■

Editor's Note: This article is reprinted here with permission from the World Health Bulletin.

State of AIDS Care 2004: One World, Multiple Standards



Forty million people are living with HIV/AIDS.

Why is it that so many are going without care?

And, for those lucky enough to access care,
to what standard is it being delivered?

Faculty:

Ernest Darkoh – *Botswana*

Paula Munderi – *Uganda*

Jean W. Pape – *Haiti*

Praphan Phanuphak – *Thailand*

Eric van Praag – *Tanzania*

Celso Ramos-Filho – *Brazil*

Julie Stachowiak – *Russia*

José M. Zuniga – *United States*

Featuring:

Jim Yong Kim – *World Health Organization*

Thursday, 15 July 2004 • 6 pm – 8 pm

IMPACT Exhibitor & Convention Center • Room K

*An official satellite meeting of the XV International AIDS Conference,
hosted by the International Association of Physicians in AIDS Care.*





MAKING RIGHT

TURNS IN THE HIV

PHARMACOLOGY

MAZE

Mark Mascolini



All roads lead to Rome, they say. But once you get there, none of them leads anywhere. At least it can seem that way to the accidental tourist or the purposeful pilgrim in town for an HIV pharmacology meeting.

The trouble is that Rome has no straight streets. That's what happens when you assemble a city on bumpy terrain over the course of several centuries and never call in a Baron Haussmann to straighten things out. As a result, it's almost impossible to find a direct route from any point A to any point B.

Take, for example, the driving directions proffered by the Cavalieri Hilton, one of the meeting hotels for the 5th International Workshop on Clinical Pharmacology of HIV Therapy, held April 1-3, 2004, in Rome. These scrupulous specs starting at the ring road include five vias, three piazzas, two piazzales, two circonvallazioni, one autostrada, two plain old roads, an array of right and left turns, and one U-turn. Online directions to another meeting hotel, the nearby Mövenpick Central Park, try to pretend you can get there from the ring road by traversing only four vias, one piazza, one circonvallazione, and one road. But we know better.

The roads to Rome may be straight and simple, but the roads in Rome are a maze.

HIV pharmacology can seem straight and simple too: "Drug A" impedes elimination of "drug B." People with crippled kidneys should get half the usual dose of "drug Z." A single nucleotide polymorphism (SNP) at gene site such-and-such favors a better response to "drug D." Or does it? As soon as pharmacology research moves from the straight-and-narrow effects of drug interactions—and sometimes even sooner—parsing results can get as perilous as plotting your course from one circonvallazione to another. U-turns are allowed but—once results are stated—rarely taken. If one learns anything from attending pharmacology workshops for a half decade, it is this: Interpretation is everything, and it's not easy.

Editor's Note: This article first appeared on HIVPharmacology.com and is reproduced here with permission.

From SNPs apparent only to real-time PCR (research has cataloged about a million) to real big differences apparent to a child—race, weight, gender, pregnancy—the human host revels in diversity. The final product, for better or worse, holds more helter and more skelter than a Roman street map, and plying those bio-byways takes the savvy, pluck, and sass of a taxi driver at rush hour.

HOW MUCH DOES THE HOST MATTER?

How much do these host factors matter in how well anti-retrovirals behave (the science of pharmacokinetic)? A lot and a little, plenty and hardly at all, depending on the variable invoked and the question ventured. And no more important question confronts HIV medicine today than how antiretrovirals—either branded or generic—will behave in millions of untreated people who could not be more diverse in size, shape, habit, habitat, and genetic heritage. This year's Pharmacology Workshop started with the good news that some of these differences matter little, if at all.

Generics and adherence in Rwanda

Rwanda, the tiny nation in East Africa's lake district that will long be remembered for the 20th century's last great (and the first televised) genocide, still faces a more insidious killer, HIV. Serge Schneider (Laboratoire National de Santé, Luxembourg) [abstract 1] listed some of the grim numbers:

- Rwanda is one of 10 African countries most heavily affected by HIV.
- A half million Rwandans have HIV infection.
- HIV prevalence stands at 11 percent.
- AIDS killed 49,000 people in 2001.
- Life expectancy has slumped from 54 to 42 years.

Recalling the Biblical heroine who forestalled a massacre, ESTHER, a collaborative effort by four European and several African and Asian countries, aims to train health-care workers, procure and maintain equipment, acquire antiretrovirals and monitor their quality, and conduct therapeutic drug monitoring (TDM). With colleagues in Luxembourg and Kigali, Schneider set out to rate the quality of generics being used in the program and reckon how well 70 people adhered to their regimens.



Testing four generic syrups, four tablets, and three capsules to see how closely antiretroviral content matched label claims, they found that levels of 13 of the 14 constituent agents lay within 10 percent of the stated amount. Among those agents with on-target drug contents were three fixed-dose combination tablets—Triviro (stavudine [d4T]/lamivudine [3TC]/nevirapine [NVP]) and Coviro (3TC plus 30 or 40 mg of d4T). One syrup, Nevimune (NVP), had only 81 percent of the claimed content.

Workers collected unannounced blood samples from 27 people taking efavirenz (EFV) and 43 taking NVP, froze the plasma, and shipped it to Luxembourg for TDM to get a snapshot of regimen adherence. Schneider reported that nine of 70 people (13 percent) had nonnucleoside levels below the low end of the therapeutic range, while the others had concentrations within or above the therapeutic range (Table 1).

The ESTHER team is measuring virologic responses in these people, but Schneider did not yet have those numbers.

GIQ predicts salvage response in the Caribbean

Earlier work by Gilles Peytavin (Hôpital Bichat-Claude Bernard, Paris) showed that a genotypic inhibitory quotient (GIQ) can predict virologic response to amprenavir/ritonavir (APV/RTV) after failure of other protease inhibitor (PI) regimens.¹ At this year's Pharmacology Workshop he showed the same is true for lopinavir/ritonavir (LPV/RTV) in heavily pretreated Caribbean patients [abstract 2].

The study involved 50 men and 24 women who had taken from one to six PIs and who had one to eight PI mutations (median 3), a median viral load of 4.6 logs, and a median CD4 count of 97 cells/ μ L. Study participants had LPV levels checked at week 2 and doses adjusted to aim for a target trough range of 3,000 to 7,000 ng/mL.

Fourteen people had LPV minimum concentrations (C_{\min} s) below 3,000 ng/mL at week 2 and had a dose change or adherence counseling. Seven people had dose changes for troughs above 7,000 ng/mL. The proportion of people with on-target LPV levels rose from 36 percent before these adjustments to 64 percent afterwards. After the dose change or counseling, 85 percent had an LPV trough above 3,000 ng/mL compared with 68 percent before those changes.

A six-month intent-to-treat analysis determined that 50 percent reached a viral load below 50 copies/mL. The median load dropped 2.79 logs in that time. Peytavin found no correlation between LPV C_{\min} or number of mutations and change in viral load at month 6. But the GIQ, defined as “LPV C_{\min} /number of LPV mutations,” did predict virologic success. Seventy-two percent of people with a GIQ above the median cutoff of 2,133 had a six-month viral load under 50 copies/mL. People with a GIQ above the median had a 2.54 times higher chance of a sub-50-copy load at month 6.

Rich, poor; female, male

Results from the studies by Schneider and Peytavin confirm that antiretrovirals—even generic antiretrovirals—follow similar pharmacologic footpaths across the world. That does not mean those pathways won't diverge once antiretrovirals reach more than a few people in poor countries and researchers plot their diverse responses. In a review lecture, Francesca Aweeka (University of California, San Francisco) listed several reasons for potential concern in poor countries:

- Higher rates of coinfection with *Mycobacterium tuberculosis* and other pathogens
- Bioequivalence and purity of generic drugs
- Drug stability in varying climates
- Biologic differences between men and women (who outnumber men with HIV in Africa)
- Racial pharmacogenomic differences

One such race-based genetic difference blipped rudely onto the pharmacologic radar at the 11th Conference on Retroviruses and Opportunistic Infections (11th CROI) earlier this year. Analysis of 190 people enrolled in ACTG A5095 found that non-Hispanic whites cleared EFV 32 percent faster (95 percent confidence interval [CI] 15 percent to 51 percent, $P < 0.001$) than blacks or Hispanics.² A second study of people in that same trial tracked changes at position 516 of the gene that codes for CYP2B6, the metabolic crankshaft for EFV.³ A TT genotype, which turned up in 20 percent of blacks and 3 percent of whites, correlated with slower clearance and higher levels of EFV, as well as with more central nervous system (CNS) side effects.

At the Pharmacology Workshop, Charles Flexner (Johns Hopkins University, Baltimore) and Courtney Fletcher

Table 1. Drug levels as a measure of adherence in 70 Rwandans

	EFV (n = 27)	NVP (n = 43)
Therapeutic range	1.0 to 4.0 mg/L	3.0 to 8.0 mg/L
Mean concentration	2.5 \pm 0.1 mg/L	9.1 \pm 5.4 mg/L
Minimum concentration	0.8 mg/L	0.0 mg/L
n below therapeutic range	4 (15%)	5 (12%)
Maximum concentration	5.8 mg/L	5.78 mg/L
n above therapeutic range	5 (18.5%)	22 (51%)



(University of Colorado, Denver) argued that such findings should not inspire a quick call for dose changes or even TDM in certain populations. If one figured the positive predictive value of a T516T genotype, Flexner noted, it would not pass muster as a diagnostic test. Efavirenz concentrations in blacks and whites in this study overlapped so much, he added, that anyone proposing TDM to all blacks taking EFV should be ready to offer TDM to all whites as well.

Fletcher called for closer collaboration between pharmacologists and statisticians to decipher the relative importance of genetic or other differences that may affect drug levels and response, as in his recent study of saquinavir (SQV) levels in women versus men.⁴

Flexner and Fletcher agreed that the question raised by such results should not be “How should this change the way I prescribe?” but “Do these results have biologic plausibility?” and “What further research will help us understand this issue better?” That research furnace is fully stoked and already sparking febrile debate. Aweeka tabulated potentially telling ethnicity data from the past few years (Table 2).

The Pharmacology Workshop offered one study of potential ethnic (and body weight) effects on antiretroviral pharmacokinetics—in Cambodians—plus several reports on another host factor that can affect antiretroviral action: coinfection with hepatitis B virus (HBV) or hepatitis C virus (HCV).

EFV concentrations and toxicity in lower-weight Cambodians

Measuring EFV levels, weight, and toxicity in 21 Cambodians and 51 French patients, Anne-Marie Taburet (Hospital Bicêtre, Paris) found higher concentrations in the lighter Cambodians but no consequent toxicities requiring lower doses [abstract 63]. The cohorts matched closely in age (median 35 years in Cambodia and 39 years in France), but the Cambodians weighed significantly less ($P < 0.05$):

- Cambodians: Median 49 kg, minimum 24 kg, maximum 62 kg
- French: Median 65 kg, minimum 34 kg, maximum 120 kg

The antiretroviral-naïve Cambodians started EFV plus d4T/3TC with a median CD4 count of 62 cells/ μ L (range 11 to 116 cells/ μ L). Steady-state EFV levels in a 12-hour post-dose sample averaged 3,580 ng/mL (median 3,133 ng/mL) in the Cambodians and 2,344 ng/mL (median 2,042 ng/mL) in the French. Two Cambodians had readings below the 1,100- to 5,000-ng/mL therapeutic range (one <50 ng/mL and one 1,073 ng/mL), and three had

levels above that range (5,286; 8,559; and 9,232 ng/mL). Higher EFV concentrations correlated with lower body weight in both groups, though the slope describing that correlation proved much steeper among Cambodians ($r^2 = 0.1934$ versus 0.0256). Nine Cambodians were taking prophylactic fluconazole, which did not affect EFV levels.

The Cambodians’

low weight reflected not only their genetic endowment but also their advanced disease. Four months of therapy boosted their weight an average 2 kg (16 kg in one 24-kg woman). Five people suffered from vertigo, which disappeared in a median of five days. Two people had transient liver cytolysis, and three had immune reconstitution flares (two tuberculosis [TB] and one *Cryptococcus meningitis*). None of the Cambodians needed to have their EFV dose trimmed.

Antiretrovirals, hepatitis, and cirrhosis

While tuberculosis, malaria, and other endemic diseases can complicate antiretroviral therapy in poor countries, in lands of plenty the co-morbidity of greatest currency is hepatitis. Several Pharmacology Workshop studies chronicled antiretroviral vicissitudes in people with hepatitis C virus (HCV) or hepatitis B virus (HBV).

High NVP levels do not drive toxicity in people with HCV
Higher pretreatment alanine or aspartate aminotransferase (ALT or AST), coinfection with HBV or HCV, higher

Table 2. Effects of ethnicity on PKs and response

Drug	Pharmacokinetics	Response
NVP	Decreased clearance in African Americans (?)	No apparent effect on toxicity
EFV	Increased concentration in African Americans ³	Increased CNS toxicity with T516T genotype ³
SQV	No data	No data
RTV	No data	No data
NFV	Decreased AUC of NFV and M8 in African Americans	No data
APV	No apparent ethnic differences*	No data
IDV	Increased AUC in African Americans in one study, and decreased AUC in African Americans in another study	CYP3A5 variants linked to antiviral response
ATV	No data	No data
LPV	No apparent ethnic differences*	No data

*Manufacturer’s information.

AUC = area under the concentration-time curve; CNS = central nervous system; M8 = principal NFV metabolite.



pretreatment CD4 count, and female gender all raise the risk of symptomatic hepatitis in people beginning NVP. But high NVP levels in people with HCV appear not to raise the toxic risk, according to results of a small comparative study by Thibaut Lavrut (University Hospital, Nice) [abstract 8].

The study involved 10 people without HCV infection and 10 with HCV and mild chronic hepatitis. The groups were similar in median age (41.5 years with HCV and 39 years without) and median CD4 count (689 cells/ μ L with HCV and 589 cells/ μ L without). Median duration of NVP therapy exceeded three years in both groups. The HCV group had a significantly higher median ALT (47 versus 25.5 UI/L) and AST (41 versus 22.5 UI/L) than the non-HCV group ($P < 0.05$ for both comparisons). But ALTs and ASTs measured less than two times the upper limit of normal in all 10 coinfecting people.

Measuring NVP levels before dosing and 1, 2, 3, 4, 6, 8, and 12 hours afterwards, Lavrut discerned no significant differences between people with and without HCV:

- Trough: 3.44 μ g/mL with HCV versus 3.39 μ g/mL without HCV
- Peak: 5.36 μ g/mL with HCV versus 5.27 μ g/mL without HCV
- Time to peak: 2.83 hours with HCV versus 2.03 hours without HCV
- Half-life: 14.04 hours with HCV versus 12.26 hours without HCV
- 12-hour AUC: 51.95 μ g \cdot h/mL with HCV versus 51.72 μ g \cdot h/mL without HCV

Lavrut concluded that the higher incidence of liver toxicity among NVP takers with HCV cannot be blamed on higher NVP levels. He proposed that clinicians can prescribe NVP at the usual dose for people with mild chronic hepatitis, as long as they consider the other precautions in prescribing this drug.

Ribavirin does not alter PKs of AZT, d4T, or 3TC

Although pegylated interferon (PegIFN) plus ribavirin yields lower sustained response rates in HCV/HIV-coinfecting people than in those with HCV alone, it is the best option for HIV-infected people who need anti-HCV therapy. Ribavirin cannot be prescribed with didanosine (ddI) because it dangerously boosts ddI's intracellular triphosphate. On the other hand, ribavirin cut intracellular phosphorylation of zidovudine (AZT), d4T, and 3TC in cell studies. But a

substudy of the international APRICOT trial found that ribavirin doesn't alter plasma or intracellular levels of those three nucleosides in people.

APRICOT randomized enrollees to one of three arms: 180 μ g of PegIFN weekly plus placebo, 180 μ g of PegIFN weekly plus 800 mg of ribavirin daily, or standard interferon plus ribavirin. The substudy presented by Jean-Michel Gries (Roche Laboratories) compared 31 people in the PegIFN/placebo group with 25 in the PegIFN/ribavirin group who were also taking AZT, d4T, and/or 3TC [abstract 4].

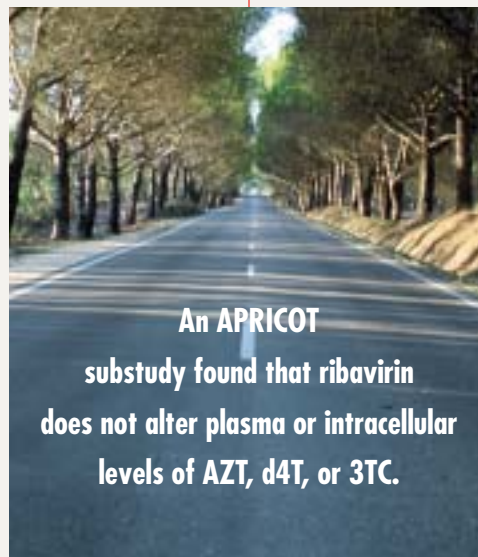
Comparing plasma levels of AZT, d4T, and 3TC before ribavirin or placebo and 12 weeks later, Gries traced virtually overlapping curves for peak plasma concentration and plasma area under the concentration-time curve (AUC). He found no significant changes in intracellular triphosphate levels of the three nucleosides after 12 weeks of either ribavirin or placebo. Nor did triphosphate levels differ much between the ribavirin group and the placebo group. Intracellular concentration-time profiles of the nucleoside triphosphates and corresponding endogenous nucleotide triphosphates varied little during 12 weeks of ribavirin therapy.

Low-dose nelfinavir effective in people with HCV and cirrhosis

Because liver impairment can slow elimination of PIs, dose reductions of indinavir (IDV), nelfinavir (NFV), LPV/RTV, and APV have been advocated. A study of 20 HCV-coinfecting people with cirrhosis found that lower doses of NFV can maintain concentrations of the PI high enough to control HIV replication.

Renato Maserati (IRCCS Policlinico San Matteo, Pavia) tracked NFV levels in four people on long-term NFV therapy and 16 just starting the PI [abstract 12]. Twelve took the full twice-daily dose, while eight started lower doses (250, 500, 750, or 1,000 mg twice daily). Measuring NFV AUC after at least 15 days of NFV therapy, Maserati adjusted the dose to aim for an AUC that fell between 45 and 75 μ g \cdot h/mL.

Eight of 12 people in the full-dose group had their NFV dose trimmed, and the group's median AUC fell from 149.5 μ g \cdot h/mL before the adjustment to 87 μ g \cdot h/mL afterwards. The median AUC measured 91.2 μ g \cdot h/mL (range 40 to 106.4 μ g \cdot h/mL) in people who started with lowered doses, and none of them had a further dose change.





After a median follow-up of 45 weeks (range eight to 208 weeks), Maserati recorded no significant changes in median:

- CD4 count: baseline 334 cells/ μ L, follow-up 388.5 cells/ μ L
- ALT: baseline 88 U/L, follow-up 65 U/L
- Total bilirubin: baseline 0.9 mg/dL, follow-up 0.8 mg/dL
- Triglycerides: baseline 183 mg/dL, follow-up 152 mg/dL
- Cholesterol: baseline 158 mg/dL, follow-up 175 mg/dL

All 10 people who started the study with a viral load below 50 copies/mL maintained that level of suppression, and four people who began with a detectable load joined the undetectable group. Slicing the NFV dose did not push up viral loads in the others. Except for three people lost to follow-up, everyone was taking NFV when Maserati made this analysis.

Lower EFV levels in people with HBV or HCV

Efavirenz levels measured eight to 14 hours after dosing proved significantly lower in people coinfecting with HBV or HCV than in those with HIV alone, according to results of a 43-person study by Rita C rte-Real (Hospital of Desterro, Lisbon) [abstract 57]. She monitored 34 men and nine women who had taken EFV for an average 19 months (range 17 to 21); 27 of them (60 percent) were taking EFV as part of their first regimen.

Among eight people coinfecting with HBV or HCV, the geometric mean EFV level measured 1.37 mg/L (95 percent CI 1.08 to 1.74 mg/L), compared with 2.06 mg/L (95 percent CI 1.87 to 2.26 mg/L) in those without HBV or HCV ($P = 0.003$). C rte-Real also found higher EFV levels in people taking tenofovir disoproxil fumarate (TDF).

PIs in children

Three Pharmacology Workshop studies scaled PI peaks and plumbed troughs in those most mercurial pharmacologic cauldrons: children.

Keeping NFV trough above 0.8 mg/L improves response

The ATHENA study showed that TDM improved virologic response in adults taking NFV,⁵ but two studies of NFV levels in children yielded contradictory results. One linked AUC with virologic response,⁶ but a second failed to confirm that finding.⁷ David Burger (University Medical Center, Nijmegen, The Netherlands) came to the Pharmacology Workshop with tie-breaking results that linked higher troughs to virologic response at treatment week 48 in 32 previously naive children [abstract 10].

The children were taking 25 to 30 mg/kg of NFV three times daily or 45 to 55 mg/kg twice daily in the PENTA 5 trial.⁸ Burger and coworkers measured morning NFV troughs after an unobserved evening dose. They set 0.8 mg/L as the lower trough threshold.

Nelfinavir troughs averaged 2.1 mg/L (coefficient of variation [CV] 65.8 percent) in the 18 children taking twice-daily NFV and 1.7 mg/L (CV 90.0 percent) in the 14 taking NFV three times daily. The two dosing groups did not differ significantly in the percentage with levels below 0.8 mg/L. Seven children (22 percent) had troughs under that threshold, with levels ranging from 0.10 to 0.57 mg/L. Fewer children with sub-therapeutic troughs had a viral load below 50 copies/mL at weeks 24 and 48 (Table 3).

Children with sub-therapeutic NFV troughs were significantly younger and weighed significantly less than children with higher troughs. Two of five children with low troughs and virologic failure at week 48 had genotyping. One had the NFV-associated L90M mutation, while the other had only secondary PI mutations—K20R, M36I, and M46L.

Burger surmised that his results may differ from those in the study that found no link between NFV levels and response⁷ for one or more reasons: a larger sample in the PENTA pharmacokinetic (PK) study, longer follow-up in PENTA, a different trough threshold (0.8 versus 1.0 mg/L), different virologic outcomes (percent below 50 copies/mL versus viral load decline), and exclusion of non-adherent children from the PENTA analysis. He proposed that 0.8 mg/L is an appropriate NFV trough for children.

Lipodystrophy and LPV/RTV troughs in kids

Children taking PIs share other similarities with adults, according to results of a 14-child study by Josep Mallolas (Hospital Clinic, University of Barcelona): LPV/RTV makes a good rescue regimen, but it pushes up lipids fast [abstract 11].

The study involved seven girls and seven boys taking 300 to 375 mg/m² of LPV/RTV twice daily after experience with more than one other PI. Their ages ranged from two to 13 years and they began LPV/RTV with a median CD4 percent of 16 percent (range 2 percent to 32 percent) and a median viral load of 5.5 logs (range 4.3 to 5.8 logs). No one had a lipid disorder before starting LPV/RTV. One girl dropped out of the study because of gastrointestinal side effects.

Table 3. **NFV troughs and sub-50-copy responses in 32 children**

	Week 24 (% <50 copies/mL)	Week 48 (% <50 copies/mL)
All children	66	69
Children with trough <0.8 mg/L	43	29
Children with trough >0.8 mg/L	72	80
<i>P</i>	0.20	0.02



By week 12, 10 of 13 children (76 percent) had a viral load below 200 copies/mL. But most paid a price for that fine response:

- Five had a total cholesterol level above 220 mg/dL
- Four (one of whom had high cholesterol) had triglycerides above 201 mg/dL
- Four (one with high cholesterol and three with high triglycerides) had clinician-defined lipodystrophy (central fat accumulation in three)

Troughs measured at least three weeks after treatment began proved significantly higher in children with a lipid disorder (8.75 µg/mL) than in those without lipid problems (3.35 µg/mL) ($P = 0.0043$). Adherence measured by questionnaire stood above 90 percent in all 13 children.

Noting that these results should be confirmed in a larger study, Mallolas suggested that TDM may be warranted to trim high LPV/RTV levels in children responding to these PIs. But this study is too small to pinpoint a trough that is safe and still effective for children with PI experience.

Once-daily LPV/RTV for children

Lower LPV/RTV doses than those used in Mallolas's study are possible in PI-naive children. And in those who control HIV well, even a once-daily dose may be feasible, reported Gwenda Verweel (Erasmus University Medical Center, Rotterdam) [abstract 60].

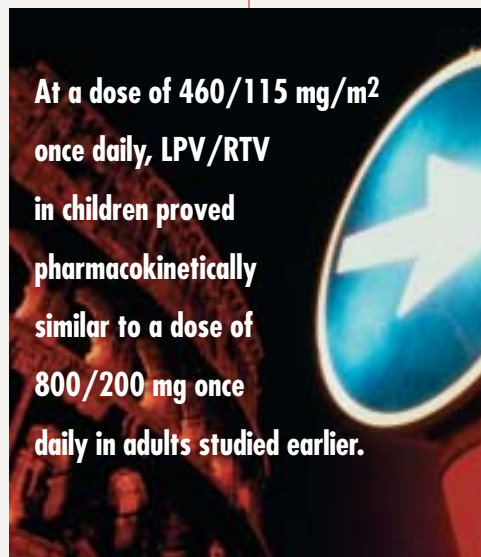
Verweel tested an LPV/RTV dose of 460/115 mg/m² once daily in seven boys and seven girls who had kept their viral load below 50 copies/mL for at least six months. Their median age stood at 4.5 years (interquartile range [IQR] 3.3 to 9.5 years), median weight at 19.9 kg (IQR 14.6 to 33.5 kg), and body surface area at 0.77 m² (IQR 0.62 to 1.11 m²). All were also taking AZT and 3TC.

The median absolute LPV/RTV dose reached 400 mg (IQR 282 to 533 mg), while the median dose per square meter reached 461 mg (IQR 448 to 483 mg). Lopinavir levels measured at steady state varied widely, but median values compared closely with those in adults taking 800/200 mg of LPV/RTV once daily,⁹ except for a somewhat lower C_{min}:

- AUC 0-24h: children 158.6 (IQR 130 to 238.5) µg • h/mL; adults 164.9 (±67.5 SD) µg • h/mL

- C_{max}: children 11.64 (IQR 9.71 to 13.40) µg/mL; adults 10.9 (±2.8 SD) µg/mL
- T_{max}: children 7.25 (IQR 4.33-12.50) h; adults 6.6 (±2.8 SD) h
- C_{min}: children 2.74 (IQR 0.65 to 9.00) µg/mL; adults 3.62 (±3.38 SD) µg/mL

Three of 14 children (21 percent) had troughs below the threshold of 1.0 mg/L and needed a dose boost; two of them were under four years old. Twelve of the 13 children maintained a viral load below 50 copies/mL through three months of treatment. The one child with a detectable load had 52 copies/mL.



Gender, pregnancy, and PKs

Happily, mother-to-child transmission of HIV has become a rarity in the industrialized world. But a few million children are already infected elsewhere. As antiretroviral access continues to improve in those HIV epicenters, mapping out the PKs of antiretrovirals in children will assume even greater urgency.

The race is already on to fill the pharmacokinetic void left by surplus enrollment of men in most trials of current antiretrovirals. And for good reason, the University of California, San Francisco's Francesca Aweeka

observed: 58 percent of infected Africans are female, as are 36 percent of infected Southeast Asians. Research already shows that SQV, NVP, LPV, and enfuvirtide (ENF) levels climb higher in women than in men, Aweeka said, while women attain lower quotients of EFV, AZT monophosphate, and AZT triphosphate. But weight, she added, can be a stronger correlate of antiretroviral exposure than gender. Pregnancy tends to taper exposure to SQV, IDV, RTV, NFV, and LPV.

A study published just before the Pharmacology Workshop detailed the effects of higher SQV levels among women than men also taking RTV or NFV in a rescue regimen.⁴ Saquinavir concentrations proved higher with RTV than with NFV. Women had higher SQV AUCs and higher C_{mins} than men did. And those higher levels made a virologic difference: 42 percent of women reached a viral load of 500 copies/mL or less by week 16, compared with 28 percent of men. Higher SQV AUC and C_{min} raised the chance of getting the viral load under 500 copies/mL ($P = 0.008$).



Lower NFV and M8 metabolite exposure in pregnancy

In his report on NFV and M8 metabolite levels during the third trimester and after delivery, Rolf van Heeswijk (Ottawa Health Research Institute) outlined the potential effects of pregnancy on antiretroviral absorption, distribution, and clearance [abstract 9]. Pregnancy may alter:

- Gastrointestinal function (for example, decreased motility)
- Body composition (for example, increased plasma volume)
- Serum albumin concentrations (which are lowered)
- Inducing or inhibiting metabolic enzymes
- Glomerular filtration rate (which is increased)

The CYP3A4 and CYP2C19 enzymes metabolize NFV, he noted, and CYP2C19 drives the formation of M8, NFV's active metabolite. Once formed, M8 is further metabolized by CYP3A4.

The study involved one Hispanic, one Caucasian, and nine black women taking 1,250 mg of NFV twice daily during pregnancy and after delivery. None were taking agents that may alter NFV's metabolism. Women had NFV and M8 levels measured before and after taking an observed dose of NFV with food at a median of 32 weeks gestation (range 31 to 36 weeks), then again a median of eight weeks after delivery (range six to 15 weeks).

Nelfinavir levels proved lower during pregnancy than after delivery, but significantly so only for the 12-hour concentration (C_{12h}):

- AUC_{0-12h} : 24 percent lower during pregnancy
- C_{max} : 19 percent lower during pregnancy
- C_{12h} : 57 percent lower during pregnancy ($P = 0.04$)

M8 levels were all significantly lower during the third trimester:

- AUC_{0-12h} : 68 percent lower during pregnancy ($P < 0.01$)
- C_{max} : 69 percent lower during pregnancy ($P < 0.01$)
- C_{12h} : 70 percent lower during pregnancy ($P = 0.02$)

Induction of CYP3A4 or inhibition of CYP2C19 could explain the low M8 values during pregnancy, van Heeswijk suggested. Although none of the women in this study had a virologic breakthrough, wide interindividual variations in NFV and M8 levels could put some women at risk of virologic failure during pregnancy. Although M8

matches NFV in antiviral potency *in vitro*, van Heeswijk noted, the clinical implications of low M8 levels are unknown.

The fault is in our genes

Had Shakespeare been our chronological as well as our psychological contemporary, he might have written in *Julius Caesar* that, "The fault, dear Brutus, is not in our stars, but in our genes." And if the Bard came to HIV meetings, he might pen a yet more trenchant trope after noting that our *stars* lie in our genes when one cites mutations such as CYP2B6*5.

Higher NFV levels linked to a solitary SNP

A SNP apparently snipped away at P-glycoprotein (P-gp) expression in people taking NFV, resulting in higher plasma and intracellular concentrations of the PI. Whether people whose lucky stars include this C-to-T SNP at position 3435 on exon 26 of the *MDR1* gene thereby benefit in CD4 gains remains controversial.

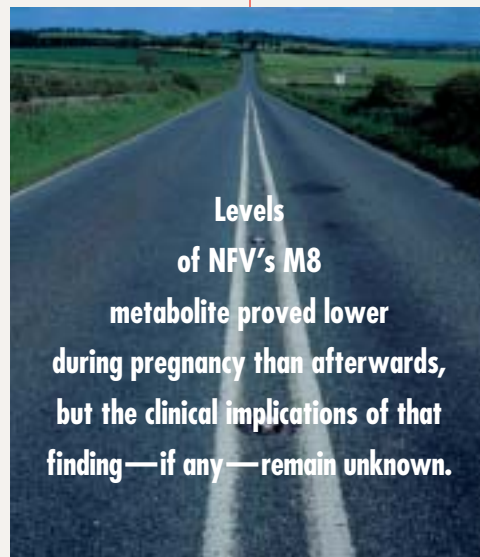
Sara Colombo (University Hospital, Lausanne) snooped for SNPs in 153 people taking NFV and 203 taking EFV [abstract 50]. Suspect SNPs at positions 3435 and 2677 did not affect EFV levels. But a shift from a CC to a TT genotype at 3435 raised plasma and intracellular levels of NFV,

as well as NFV accumulation measured as intracellular-to-plasma ratio:

- Median plasma AUC 1.3 times higher with TT than CC, $P = 0.07$ (Wilcoxon)
- Median intracellular AUC 2.1 times higher with TT than CC, $P = 0.02$ (Kruskal-Wallis)
- Median intracellular-to-plasma ratio 1.4 times higher with TT than CC, $P = 0.01$ (Wilcoxon)

The results make genetic sense, Colombo argued, because NFV is a P-gp substrate and EFV is not. Expression of the P-gp drug pump on pharmacologically critical tissues and T cells is lower in people with the 3435TT genotype, so more NFV can pile up in their T cells.

But does the measured difference in NFV concentrations explain the better CD4 response seen in people with the TT genotype?¹⁰ Not everyone is ready to buy that logic, including Charles Boucher (University of Utrecht, The Netherlands), who claimed he had "a hard time





convincing myself⁹ that small differences in NFV exposure would translate into big gains in CD4 cells.

PHARMACOLOGY NEWS ON NEW ANTIRETROVIRALS

There's nothing like a new drug to get a pharmacologist's creative juices flowing, especially when that drug leaves the cosseted confines of controlled trials and starts getting used by thousands of people who may claim exactly those traits that kept them out of trials. This year's Pharmacology Workshop featured dozens of reports on recently approved antiretrovirals including TDF, ENF, and atazanavir (ATV).

Among the investigational agents spotlighted were the PIs tipranavir (TPV) and TMC114, the co-receptor antagonists AMD070 and UK-427,857, and the NRTI elvucitabine. These headlines emerged:

- A multicenter cohort study challenged earlier evidence that TDF lowers levels of ATV, while another study found non-significantly lower ATV exposure with TDF.
- Tenofovir and abacavir (ABC) do not antagonize each other inside cells, a mechanism suggested for failure of triple-nucleoside regimens including those two drugs.
- Enfuvirtide levels proved lower in two clinic studies than they did in trials.
- If it gets licensed, elvucitabine could be the world's first once-weekly antiretroviral.

Tenofovir disoproxil fumarate

Tenofovir won the Pharmacology Workshop's sweepstakes as the most-studied drug, beginning with the news that it may not consistently lower levels of ATV, as previously reported, and ending with the first good look at its much anticipated coformulation with emtricitabine (FTC).

Are ATV troughs lower with TDF?

Earlier work found lower troughs of the once-daily PI ATV when given with TDF, whether boosted by RTV¹¹ or not.¹² With RTV and TDF, ATV's C_{min} was 26 percent lower than normal,¹¹ and with TDF but without RTV the trough was 39 percent lower than normal.¹² But a study of people prescribed various doses of ATV at 31 German clinics did not confirm those findings. A smaller Italian study found substantially (but not significantly) lower ATV levels with TDF than without it.

Guido Kruse (HIV-Lab, Berlin) evaluated 178 plasma

samples from people taking ATV with or without TDF in one of seven doses [abstract 49]:

- 400 mg with 300 mg of TDF ($n = 11$)
- 300 mg with 100 mg of RTV ($n = 26$)
- 300 mg with 100 mg of RTV and 300 mg of TDF ($n = 53$)
- 300 mg with 2,000 mg of SQV and 100 mg of RTV ($n = 56$)
- 300 mg with 2,000 mg of SQV and 200 mg of RTV ($n = 7$)
- 300 mg with 800 mg of LPV and 200 mg of RTV ($n = 16$)
- 300 mg with 2,000 mg of SQV, 800 mg of LPV, and 200 mg of RTV ($n = 9$)

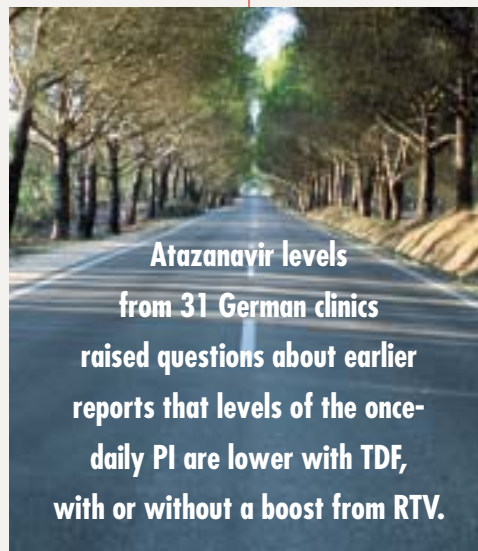
Kruse used samples collected between 23 and 25 hours after ATV dosing to figure ATV troughs and samples collected between 11 and 13 hours after dosing to figure troughs of other PIs.

First, the analysis showed that German clinicians usually give ATV with an RTV boost and often with a boost plus a second PI, either SQV or LPV. Only 11 of the 178 samples studied (6 percent) came from people taking unboosted ATV. Those 11 people all took ATV with TDF, and their mean ATV trough measured 148 ng/mL (95 percent CI 75 to 291 ng/mL). That mean exceeded the trough of 120 ng/mL without TDF listed in ATV product information

and more than doubled the 70-ng/mL trough found with TDF in healthy volunteers.¹³

Among 53 people taking 300/100 mg of ATV/RTV plus TDF, the ATV trough averaged 576 ng/mL (95 percent CI 469 to 713 ng/mL). In 26 people taking 300/100 mg of ATV/RTV without TDF, the average ATV trough stood at 567 ng/mL (95 percent CI 416 to 773 ng/mL). Both of those mean troughs lie above the trough of 491 ng/mL reported earlier for ATV/RTV with TDF.¹¹ Kruse argued that the fairly large number of samples in his analysis of people taking boosted ATV with or without TDF inspire confidence in the reliability of these results. With either regimen, though, the troughs varied substantially from one person to the next.

Elena Seminari (San Raffaele Hospital, Milan) did find lower ATV troughs when people took the PI with TDF [abstract 22]. No one in this study used an RTV boost, but some took APV (600 mg twice daily or 1,200 mg once daily) as a second PI. These 32 heavily pretreated people received 400 mg of ATV as part of an expanded access program. No one took an NNRTI.





Measuring ATV levels after at least two weeks of treatment, Seminari found lower median troughs with TDF than without it, and the troughs with TDF were much lower than the 148 ng/mL average Kruse found in people taking unboosted ATV with TDF:

- ATV with TDF (without APV) ($n = 12$): 108 ng/mL (range 20 to 950 ng/mL)
- ATV without TDF (without APV) ($n = 8$): 200 ng/mL (range 66 to 584 ng/mL)
- ATV with TDF (with APV) ($n = 9$): 73 ng/mL (range 0 to 418 ng/mL)
- ATV without TDF (with APV) ($n = 3$): 213 ng/mL (range 114 to 284 ng/mL)

The trough differences with and without TDF did not reach statistical significance, perhaps because of the small number of people studied. Inpatient ATV trough variability proved higher with TDF and APV (coefficient of variation [CV] 51 percent, range 11 percent to 141 percent) than with TDF but without APV (CV 30 percent, range 2 percent to 91 percent). Amprenavir lowered ATV's peak and AUC but had little effect on ATV's trough concentration.

In Kruse's study, ATV troughs averaged 818 ng/mL (95 percent CI 692 to 967 ng/mL) in 56 people taking the PI with 100 mg of RTV and 2,000 mg of SQV, and 824 ng/mL (95 percent CI 537 to 1,263 ng/mL) in seven people taking the same doses of ATV and SQV with 200 mg of RTV. Those troughs came close to the 767 ng/mL reported earlier with a once-daily 300/100/1,600-mg dose of the three PIs.¹⁴ Saquinavir's trough with 300/100 mg of ATV/RTV averaged 448 ng/mL (95 percent CI 338 to 593 ng/mL).

Mean LPV troughs stood at 3,155 ng/mL (95 percent CI 2,310 to 4,310 ng/mL) in 16 people taking 300/800/200 mg of ATV/LPV/RTV and 3,707 ng/mL (95 percent CI 2,482 to 5,537 ng/mL) in nine people taking the same doses of those PIs plus 2,000 mg of SQV. Those LPV levels fell short of the 5,500 ng/mL reported with 400/100 mg of LPV/RTV twice daily,¹⁵ but Kruse noted that no one has reported evidence of an interaction between LPV and ATV.

No interactions between SQV/RTV and TDF

Jintanat Ananworanich (HIV-NAT, Bangkok) found no

SQV C_{min} change after 14 people switched from ddI/d4T to 3TC/TDF [abstract 27]. Indeed, fewer people had suboptimal SQV C_{mins} after they started TDF.

Using the SQV hard-gel capsule (HGC), five men and nine women had begun once-daily SQV/RTV (1,600/100 mg) with ddI (250 or 400 mg once daily depending on weight) and d4T (30 or 40 mg twice daily depending on weight). The HIV-NAT team measured SQV troughs after people took that regimen for at least eight weeks. Everyone later traded ddI/d4T for once-daily 3TC/TDF (300/300 mg) and had repeat trough testing after at least eight weeks of the new regimen. Body weight did not

differ significantly from the time of the first trough reading (median 55.5 kg, interquartile range [IQR] 47.8 to 60.8 kg) to the time of the second reading (median 55.1 kg, IQR 49.2 to 61.7 kg). The median time on SQV measured 14 months (IQR seven to 18 months) when they had their second trough measure.

Mean and median SQV troughs both rose non-significantly after the switch to TDF (Table 4).

TDF did not alter 24-hour concentration-time profiles of SQV HGC at a twice-daily RTV-boosted dose of 1,000/100 mg in a 14-day study involving 18 people, reported Marta Boffito (Chelsea and Westminster Hospital, London). Nor did SQV change two-day or 13-day levels of

TDF [abstract 31].

Boffito studied 14 men and four women with tight viral control while taking an SQV/RTV regimen. They had PK sampling on study day 1 (before adding TDF), day 3 (one day after adding TDF), and day 14 (13 days after adding TDF). Tenofovir levels proved similar to those recorded in a single-dose TDF study on both day 3 and day 14. Boffito detected no change in TDF AUC, C_{max} , trough, half-life, or time to maximum concentration from day 3 to day 14.

No intracellular ABC-TDF antagonism

Surely the biggest antiretroviral disappointment of this young century (aside from skimpy access in most poor countries) is the triple failure of triple regimens containing TDF, ABC, and 3TC taken once daily,¹⁶⁻¹⁸ along with suboptimal potency^{19,20} or out-and-out inanity²¹ of other nuke troikas. Many experts fingered a low genetic barrier to resistance via the mutations M184V and K65R as a prime suspect in the untimely demise of regimens combining

Table 4. SQV troughs with ddI/d4T versus 3TC/TDF

	With ddI/d4T	With 3TC/TDF
Mean (SD) C_{min} (mg/L)	0.34 (0.35)	0.48 (0.58)
Median (IQR) C_{min} (mg/L)	0.28 (0.16 to 0.37)	0.31 (0.12 to 0.51)
Minimum C_{min} (mg/L)	0	0.08
Maximum C_{min} (mg/L)	1.36	2.12
Coefficient of variation	103%	120%
$C_{min} \leq 0.05$ mg/L (% , n)	14.3 (2)	0
$C_{min} \leq 0.1$ mg/L (% , n)	21.4 (3)	7.1 (1)

IQR = interquartile range; SD = standard deviation.



TDF, ABC, and/or ddI. But other possibilities—including intracellular antagonism between TDF and ABC—had to be explored. After all, inside-the-cell incompatibility undid AZT/d4T. But two Pharmacology Workshop reports ruled out the TDF-ABC antagonism hypothesis.

Arnold Fridland (Gilead Sciences) measured phosphorylation of ABC to carbovir triphosphate and of TDF to tenofovir diphosphate in peripheral blood mononuclear cells (PBMCs) from healthy volunteers and in CEM cells [abstract 5]. At concentrations of 10 μM and 100 μM (much higher than plasma concentrations in humans), neither TDF nor ABC inhibited intracellular phosphorylation of the other drug. Using the same CEM cell model, Fridland showed that 3TC slices ddC triphosphate levels by 75 percent.

Trevor Hawkins (Southwest CARE Center, Santa Fe, New Mexico) measured tenofovir diphosphate and carbovir triphosphate directly in PBMCs from 15 people taking ABC/TDF with 3TC or d4T [abstract 2.4]. He collected samples while people were taking the ABC/TDF regimen, then for 28 days after eight people traded TDF for a new drug and seven switched from ABC to another antiretroviral. Withdrawing either reverse transcriptase inhibitor had no effect on intracellular sums of the other agent's metabolite over the 28 days of study.

The intracellular half-life of carbovir triphosphate ranged from 12 to 19 hours, while the half-life of tenofovir diphosphate exceeded 60 hours. Hawkins found less interpatient and inpatient variability with tenofovir diphosphate than with carbovir triphosphate.

Do these findings clinch the case against resistance as the sole culprit in failures of TDF, ABC, and 3TC? Not completely, the University of Utrecht's resistance sage Charles Boucher argued in a review lecture. Among people genotyped after failure of that triple regimen, 64 percent had both the M184V and K65R mutations. Together, Boucher reasoned, those two resistance rousers are enough to cripple all three drugs.

But 36 percent of people in whom the regimen foundered had only the M184V (or I) mutation—without K65R. Phenotypic studies show that this virus should remain susceptible to TDF. Indeed, position 184 mutants should be *hypersusceptible* to TDF. And TDF monotherapy can peel 1.5 logs off a high viral load. But the regimen flopped anyway. To Boucher, that must mean these people had too little tenofovir diphosphate in their cells to counter the M184V/I mutant.

The same rationale may explain some failures of other regimens—AZT/3TC/ABC, AZT/3TC/NFV, AZT/3TC/NNRTI—in which genotyped virus had mutations that confer resistance to some, but not all drugs in the regimen. In cases like these, Boucher argued, drugs to which the mutant virus remains susceptible may fail to reach inhibitory levels in cells or some other critical compartment.

High TDF levels in a person with renal insufficiency

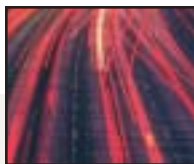
Although rare, renal insufficiency with renal tubular dysfunction has troubled people taking TDF,²²⁻²⁴ and TDF combined with LPV/RTV may explain one case of Fanconi syndrome.²⁵ A Pharmacology Workshop case report by Milly Hillebrand-Haverkort (Onze Lieve Vrouwe Gasthuis, Amsterdam) appears to be the first linking high plasma TDF to renal insufficiency, and again the patient was also taking LPV/RTV [abstract 72].

With a CD4 count of 60 cells/mm³, a 54-year-old man was taking TDF, d4T, ABC, EFV, and APV. A relentlessly rising viral load prompted his clinician to add four capsules of LPV/RTV twice daily. That prescription rose to five capsules twice daily when the man failed to achieve adequate LPV levels with the four-capsule dose. Three months later he traded d4T for 3TC, and two weeks after that he was admitted to the hospital with abdominal pain and dyspnea diagnosed as renal insufficiency (serum creatinine 374 $\mu\text{mol/L}$, hyperphosphatemia at 2.2 mmol/L, and metabolic acidosis). Serum creatinine rose to 447 $\mu\text{mol/L}$ as the patient continued his antiretrovirals during the hospital evaluation. At that point clinicians stopped all antiretrovirals and creatinine fell to 129 $\mu\text{mol/L}$. When the same regimen (minus 3TC) resumed, creatinine climbed back to 172 $\mu\text{mol/L}$. When 3TC replaced TDF, creatinine fell to normal levels.

This man was also taking seven other potentially nephrotoxic drugs, but he had taken them for years at the same dose with no problem. Because LPV/RTV boosts TDF exposure, Hillebrand-Haverkort measured TDF in frozen plasma samples from this patient. Tenofovir levels measured six to seven hours after dosing rose inexorably with LPV/RTV:

- Before LPV/RTV: 0.047 mg/L
- With four LPV/RTV capsules: 0.247 mg/L
- With five LPV/RTV capsules: 0.359 mg/L

Independent studies ruled out the possibility of intracellular antagonism between ABC and TDF. But the findings do not mean resistance is the only explanation for failures of triple-nuke ABC/TDF regimens.



Renal clearance of TDF fell from 115 to 55 mL/min after LPV/RTV got added to the mix.

Because this case report and others suggest that renal dysfunction may be a cumulative dose-dependent effect of TDF, especially when taken with LPV/RTV, Hillebrand-Haverkort believes continuous monitoring of renal function makes sense for people taking the drug. Tenofovir drug monitoring may help single out people with a high risk of kidney problems, she added. “A significant increase in TDF serum concentrations, even in patients with normal levels, should warn the physician,” she proposed. “To prevent [TDF] accumulation, dose reduction should be considered in such cases, even if renal clearance still exceeds 50 mL/min.”

Higher EFV concentrations with TDF

As summarized earlier in this article, a study presented at this year’s Pharmacology Workshop found significantly lower EFV levels in people coinfecting with HBV or HCV. The same study, presented by Rita Côrte-Real (Hospital of Desterro, Lisbon), found higher EFV concentrations in people taking the nonnucleoside with TDF than in those taking it with nucleosides or PIs [abstract 57].

The analysis involved 45 people taking EFV for six months or more; 19 of them also had TDF prescriptions. Collecting two to seven samples from each person eight to 14 hours after EFV dosing, Côrte-Real measured the following geometric mean EFV levels (and 95 percent CIs):

- EFV with NRTIs and TDF: 2.10 mg/mL (1.45 to 3.05 mg/mL)
- EFV with NRTIs and PIs: 1.95 mg/mL (1.28 to 2.97 mg/mL)
- EFV only with NRTIs: 1.88 mg/mL (1.75 to 2.04 mg/mL)

The difference between the TDF group and the nucleoside-only group was statistically significant ($P = 0.029$).

TDF/FTC: One pill once a day

Fixed-dose confections of two or three antiretrovirals have become mainstays of generic makers’ product lines. But so far competition between brand name houses has limited antiretroviral coformulations to two all-in-the-family combos—Combivir and Trizivir—while 3TC/ABC and TDF/FTC pick their way across the pharmacologic proving grounds. Brian Kearney (Gilead Sciences) came to the

Pharmacology Workshop with a progress report on TDF/FTC, and the news was good [abstract 62]. The once-a-day pill, about as big as a standard hefty multivitamin, yielded concentrations of its constituents equivalent to those of the single-drug pills now on the market.

The single-dose crossover study measured levels of the individual drugs dosed together and, one week later, of the coformulated capsule. The 44 healthy volunteers—26 men and 18 women—had an average age of 43.6 years (± 10.8 SD) and weight of 76.5 kg (± 10.1 SD). Five people dropped out of the study, none with grade 3 or 4 toxicity and only one with a problem attributed to study drugs—a mild rash.

In blood samples collected 48 hours after dosing, Kearney found nearly identical TDF and FTC peaks, AUCs, and half-lives with the individual drugs and the fixed-dose combination.

HIV sparks a key nucleoside activator

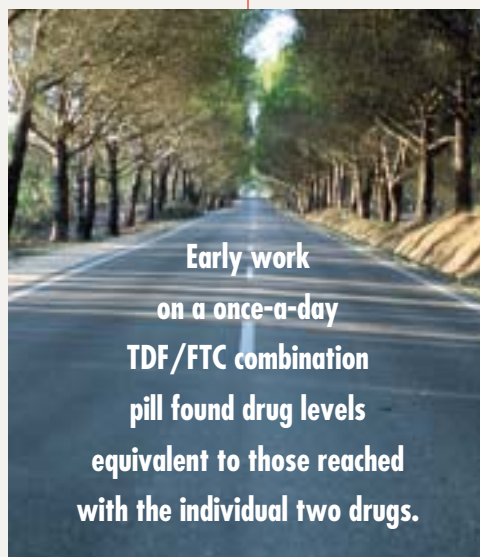
Levels of the nucleoside activator thymidine kinase (TK) are significantly higher and vary more widely in people with HIV infection than in uninfected individuals. Guido Antonelli (University La Sapienza, Rome) reached those conclusions after gauging TK levels in PBMCs from 46 antiretroviral-naïve people with HIV infection and from 10 healthy volunteers without HIV or other infections and taking no drugs [abstract 7].

Thymidine kinase activity proved significantly higher in the HIV group whether Antonelli used AZT or 3TC as a substrate for the enzyme. Thymidine kinase activity also ranged widely in people with HIV infection and much less so in the uninfected controls. Deoxycytidine kinase activity varied more widely in people with HIV than in healthy controls, but mean activity was not significantly higher in the HIV group (Table 5).

Antonelli urged colleagues to probe for viral or cellular factors that may contribute to these differences in people with HIV and to explore the effects of such factors on response to antiretroviral therapy.

Enfuvirtide

Despite its steep price and multistep, twice-daily injection schedule, ENF has gained adherents among those who can add it to a regimen including one or more active drugs. Now that this pioneer fusion inhibitor has reached a wider clinic population, however, two studies suggest that ENF levels are not measuring up to those reported in





clinical trials. And one of these studies turned up evidence that nodules formed at injection sites could contribute to low blood levels. Whether such results support TDM for ENF is another question.

Lower ENF concentrations seen in the clinic

Stefano Bonora (University of Torino, Italy) studied 22 men and four women who started ENF with a median CD4 count of 77 cells/ μ L and a median viral load of 4.8 logs while taking a median of three other antiretrovirals (range two to four) [abstract 46]. Comparing ENF concentrations on treatment day 2 and treatment day 14, Bonora found a significantly lower mean trough and a marginally lower mean AUC on the second reading:

- Trough: Day 2, 2,926 \pm 1,469 ng/mL; day 14, 2,318 \pm 1,245 ng/mL ($P = 0.03$)
- AUC: Day 2, 49,745 \pm 17,707 ng \cdot h/mL; day 14, 45,633 \pm 16,239 ng \cdot h/mL ($P = 0.06$)

The day 2 trough comes close to the 3,300 ng/mL listed in product literature, while the day 14 trough reflects a significant falloff. Bonora suggested these findings mean several days of ENF therapy must pass before levels reach a steady state.

Ten people (38 percent) had a minimum effective concentration below a target of 1,000 ng/mL, and 13 percent of all troughs measured fell below that threshold. The coefficient of variation for interindividual variability in ENF troughs was 71 percent, while intraindividual variability measured 38 percent.

About 65 percent of people taking ENF get injection site nodules or cysts, and earlier immunoperoxidase staining studies showed that the drug can pool in these lesions.²⁶ Wondering whether nodules explained ebbing ENF levels in these people, Bonora compared concentrations in people with and without nodules. Median and mean troughs proved lower in 65 samples from people with nodules than in 44 samples from those without them, but these differences fell short of statistical significance ($P = 0.18$ for medians and $P = 0.15$ for means).

Analysis of ENF quotients in 19 people on day 14 found no significant difference in troughs or peaks in seven with nodules versus 12 without them. But the mean AUC stood significantly lower in people with nodules (39,450 \pm 14,433 versus 50,041 \pm 14,052 ng \cdot h/mL, $P = 0.04$).

Hartmut Stocker (Vivantes Auguste-Viktoria Klinikum, Berlin) also found a lower mean trough in 39 people taking ENF than the trough listed in product literature (2,030 versus 3,300 ng/mL) [abstract 45]. Comparing 15 people with the highest troughs (above 2,410 ng/mL) and 15 with the lowest (below 1,750 ng/mL), he found a substantially lower median CD4 count (50 versus 182 cells/ μ L) and higher viral load (5.4 versus 4.5 logs) in those with the low troughs. The coefficient of variation for interindividual variability in troughs proved much lower in Stocker's study (8.5 percent) than in Bonora's (71 percent) but still comparable with interindividual

variability in troughs of LPV (8.1 percent) and NFV (8.8 percent).

Stocker suggested several possible reasons for lower ENF readings in the clinic than in trials:

- Limited stability of ENF in serum samples
- Lower ENF levels in serum than in EDTA plasma
- Greater patient difficulty in handling ENF outside clinical trials

- Unidentified interactions
- Higher prevalence of conditions like wasting, thyroid disease, or nephritic syndrome in the general HIV population than in clinical trial populations

Because of interindividual variability in troughs and scant data on the effect of drug interactions or comorbidities, Stocker advocated TDM for ENF. Bonora also endorsed TDM for the fusion inhibitor, citing interpatient variability and suboptimal troughs seen in some people. Others, such as John Gerber (University of Colorado, Denver), evinced less enthusiasm for ENF TDM at this point. Gerber called for more study of how ENF samples should be collected and stored and for ENF assay proficiency testing in TDM labs.

Atazanavir

The most surprising Pharmacology Workshop news on ATV came in the 31-clinic study that found good troughs of the PI when given with TDF—a finding at odds with earlier reports (see “Tenofovir disoproxil fumarate” section above). Other Pharmacology Workshop studies suggested a role for TDM when prescribing ATV and described one ATV combination that did not work well.

Table 5. **Thymidine or deoxycytidine kinase activity and variability in people with or without HIV**

	Substrate	HIV+	CV (%)	HIV-	CV (%)	P
TK activity (mean \pm SD U/mg of protein)	AZT	0.39 + 0.34	87.2	0.12 + 0.25	20.5	0.017
TK activity (mean \pm SD U/mg of protein)	3TC	3.79 + 3.85	>100	0.68 + 0.26	38.2	0.014
dCK activity (mean \pm SD U/mg of protein)	Cytidine	2.90 + 1.62	56.0	3.94 + 0.59	15.0	0.054

CV = coefficient of variation; dCK = deoxycytidine kinase; TK = thymidine kinase.



Lower once-daily SQV levels with ATV

A small study discussed above found that APV at a dose of 600 mg twice daily or 1,200 mg once daily lowered ATV's peak concentration (median 2,990 ng/mL with APV and 5,170 ng/mL without APV) and AUC (median 23,980 ng•h/mL with APV and 33,400 ng•h/mL without APV) but had little effect on ATV troughs or clearance (see "Tenofovir disoproxil fumarate" section above). A 400- or 600-mg dose of ATV plus 1,200 mg of SQV HGC proved safe and comparable to RTV/SQV (400/400 mg twice daily) as a rescue regimen in one published trial.²⁷ But SQV troughs proved low with this double-PI regimen in two other studies.^{28,29} At this year's Pharmacology Workshop, Francesca Canta (University of Torino, Italy) confirmed low SQV exposure with ATV and a trend to low ATV troughs as well [abstract 33].

The study involved 21 people with an average age of 49 years enrolled in an ATV expanded access program. Seven took 400 mg of ATV plus 1,200 mg of SQV HGC once daily plus one nucleoside, while 14 took ATV plus two nucleosides without SQV. No one in either group took a nonnucleoside or other drugs that may muddle metabolism of the two PIs. The 14 people in the ATV-only group included five women, while all seven people in the ATV/SQV group were men. The median baseline viral load stood at 1.98 logs in the ATV-only group versus 4.49 logs in the dual-PI group. Neither of these differences reached statistical significance. About half in each group had HCV coinfection.

Steady-state drug level readings showed a non-significantly lower mean ATV trough in the ATV/SQV group (86 ng/mL, range 5 to 316 ng/mL) than in the ATV-only group (205 ng/mL, range 5 to 920 ng/mL, $P = 0.25$). Four of seven (57 percent) in the double-PI group and two of 14 (14 percent) in the single-PI group had an ATV trough below 14 ng/mL, the 90 percent inhibitory concentration for wild-type virus, but this difference also lacked statistical significance ($P = 0.12$). The SQV trough in the dual-PI group averaged 46 ng/mL (range 5 to 310 ng/mL), and six of those seven people (86 percent) had an SQV trough below a minimum effective concentration of 100 ng/mL.

Canta advised clinician colleagues to avoid once-daily ATV/SQV (400/1,200 mg), though the interaction between these PIs probably needs further study. In a 20-person trial, adding 300 mg of ATV to 1,600/100 mg of once-daily SQV/RTV significantly boosted SQV's AUC by 60 percent, its peak by 42 percent, and its trough by 112 percent ($P < 0.05$).¹⁴

High ATV exposure predicts high bilirubin

Two studies tied higher ATV concentrations to a greater risk of hyperbilirubinemia, and both study teams suggested that TDM may help predict this risk.

Daniel González de Requena (University of Torino, Italy) tracked ATV and bilirubin levels in 31 men and 14 women taking 400 mg of the PI without RTV in an expanded access program [abstract 58]. Their median age was 42 years, and 19 (42 percent) had coinfection with HCV or HBV.

After four weeks of treatment, 36 (80 percent) had a viral load below 50 copies/mL or more than a 1-log drop in viral load. Pretreatment ATV-linked mutations did not affect virologic response, but ATV concentrations did. The four-week drop in log viral load correlated inversely with C_{max} ($r = -0.547$, $P = 0.023$) and 24-hour AUC ($r = -0.5$, $P = 0.049$) but not with C_{min} . Area under the curve also correlated with percent gain in CD4 cells.

The percentage of people with total and unconjugated bilirubin levels above 1 mg/dL rose substantially after four weeks of ATV, but no one had a conjugated bilirubin level above

that threshold at either point (Table 6).

Atazanavir C_{min} correlated positively with the percent of total bilirubin change from baseline ($r = 0.47$, $P = 0.013$). And C_{min} ($r = 0.44$, $P = 0.02$), C_{max} ($r = 0.43$, $P = 0.04$), and AUC ($r = 0.42$, $P = 0.05$) correlated with percent change in unconjugated bilirubin. Linear regression analysis including baseline total and unconjugated bilirubin, HCV coinfection, and ATV C_{min} , C_{max} , and AUC singled out AUC as the only independent predictor of percent gain in total and unconjugated bilirubin.

González proposed that TDM could help improve the early response to ATV while enhancing the drug's safety. Whether the same proves true with RTV-boosted ATV—the way most people will take this PI—awaits further study.

Sonia Rodríguez-Novoa (Carlos III Hospital, Madrid) also mapped bilirubin changes in people taking 400 mg of unboosted ATV [abstract 55]. Studying 48 men and 20 women, 44 percent of whom had HCV coinfection, she found higher 12-hour concentrations of the PI after 12 weeks of therapy in people with hyperbilirubinemia.

By week 12, the median AST rose 15.2 U/L and the median ALT climbed 2.4 U/L. Neither change was significant and neither correlated with HCV status. Median total cholesterol fell 9.8 mg/dL by week 12 ($P = 0.007$), while median triglycerides dropped 20.6 mg/dL ($P < 0.001$). Atazanavir concentrations did not correlate with lipid changes.

Table 6. Bilirubin changes after four weeks of unboosted ATV (n = 45)

	Total bilirubin >1 mg/dL	Unconjugated bilirubin >1 mg/dL	Conjugated bilirubin >1 mg/dL
Baseline (% patients)	11.4	4.5	0
Week 4 (% patients)	61.8	44.1	0



Bilirubin rose in 70 percent of study participants, and 11 percent had a grade 4 elevation (above 3.9 mg/dL). Median 12-hour ATV levels proved significantly higher in people with hyperbilirubinemia (0.82 µg/mL) than in those without it (0.22 µg/mL, $P = 0.006$), though confidence intervals in this comparison overlapped substantially.

Tipranavir and TMC114

Two protease inhibitors within sight of the clinic, TPV and TMC114, both stifle PI-resistant virus. One Pharmacology Workshop study rated TPV/RTV in deep salvage, while another gauged its interactions with atorvastatin and antacids. A third study plotted the PKs of TMC114/RTV.

Rebound after good early response to TPV/RTV plus another PI

Tipranavir/RTV at a dose of 500/200 mg twice daily has reached phase 3 trials. That dose may fall short for people rich in PI experience, even when they add a third PI, suggest preliminary results presented by Kevin Curry (Boehringer Ingelheim) [abstract 34].

This trial enrolled 296 people, mostly white men, whose charts included triple-class failure, failure of two or more PI regimens, three or more protease mutations at positions 33, 82, 84, or 90, and a viral load above 1,000 copies/mL. In fact, the median viral load approached 100,000 copies/mL, while the median CD4 count stood at 140 cells/µL (range 0 to 867 cells/µL). Experience with PIs does not get much deeper than this.

Curry and colleagues randomized these people to one of four regimens:

- TPV/RTV 500/200 mg twice daily
- SQV/RTV 1,000/100 mg twice daily
- APV/RTV 600/100 mg twice daily
- LPV/RTV 400/100 mg twice daily

After two weeks, everyone not taking TPV added TPV/RTV 500/100 mg twice daily. Investigators picked the other drugs to go with the PIs. Similar proportions in each arm (from 11 percent to 18 percent) added ENF. After two weeks, 55 percent to 60 percent in each group had some side effect, usually diarrhea (5.3 percent with SQV, 10.1 percent with LPV, 13.6 percent with TPV, and 15.8 percent with APV).

At the two-week point people taking TPV/RTV

enjoyed the biggest viral load drop—a median of 1.2 logs compared with 0.2 with APV/RTV, 0.3 with SQV/RTV, and 0.4 with LPV/RTV. When people taking APV, SQV, or LPV added 500 mg of TPV and an extra 100 mg of RTV, the median viral load dipped to 1.2 logs below baseline in the next two weeks. But viral loads began to rebound after that. By week 8, the median drop from baseline stood at about 0.5 log with TPV/RTV, about 0.8 log with SQV/RTV/TPV and LPV/RTV/TPV, and about 0.9 log with APV/RTV/TPV.

Dwindling PI concentrations may have helped propel these rebounds in the triple-PI groups. Adding TPV at week 2 cut LPV's trough by about 45 percent, APV's by about 50 percent, and SQV's by about 80 percent. Peak concentrations and AUCs of the third PIs also fell when they teamed up with TPV. The CYP3A4-inducing effect of TPV may have undercut the inhibiting effect of RTV, although in a study of healthy volunteers a single dose of TPV/RTV (500/200 mg) nearly completely inhibited hepatic CYP3A4 activity (see next section). Further analysis of this salvage trial should pick out factors that favored rebounds or a more durable response.

Interactions between TPV/RTV and atorvastatin or antacids

TPV/RTV (500/200 mg) jacked up exposure of atorvastatin nearly 9-fold, while the antacid Maalox lowered TPV concentrations by up to 29 percent in a study of 23 healthy volunteers by Ottawa Hospital's Rolf van Heeswijk [abstract 35]. He gauged the effect of the three drugs in 12 women and 11 men with a median age of 32 years (range 18 to 55 years) and a median weight of 72 kg (range 55 to 99 kg). The intricate 22-day study design measured drug concentrations at the following points:

- Day 1: single-dose PKs of atorvastatin (40 mg)
- Day 8: single-dose PKs of TPV (500 mg plus 200 mg RTV)
- Day 13: single-dose PKs of TPV (500 mg plus 200 mg RTV plus antacid)
- Day 19: steady-state PKs of TPV (500 mg plus 200 mg RTV)
- Day 20: single-dose PKs of atorvastatin (10 mg plus 500/200 mg TPV/RTV at steady state)
- Day 20: steady-state PKs of TPV (500 mg plus 200 mg RTV plus 10 mg atorvastatin)

For people with deep PI experience, TPV plus a second PI boosted by RTV yielded a transient 1.2-log drop in viral load through eight weeks of follow-up.



The geometric mean single-dose AUC of atorvastatin rose from 89.3 h•ng/mL on day 1 (40 mg without TPV/RTV) to 209 h•ng/mL on day 20 (10 mg with steady-state TPV/RTV). Atorvastatin's dose-normalized day-20 AUC (figured by multiplying the day 20 value by 40/10 mg) was 836 h•ng/mL (range 478 to 1,850 h•ng/mL). The geometric mean C_{max} climbed from 17.6 ng/mL on day 1 to a dose-normalized 151 ng/mL (range 80.0 to 345 ng/mL) on day 20 with the steady-state PIs. The statin's 12-hour level jumped from 2.25 ng/mL on day 1 to a dose-normalized 11.7 ng/mL on day 20 with the PIs. Atorvastatin had no apparent effect on TPV levels. Van Heeswijk rated the atorvastatin surges "clinically relevant" and recommended close monitoring of people who take the statin with TPV/RTV.

Geometric mean ratios of TPV/RTV plus antacid to TPV/RTV alone showed substantial drops in TPV exposure:

- AUC: 0.73 (90 percent CI 0.64 to 0.84)
- C_{max} : 0.75 (90 percent CI 0.63 to 0.88)
- C_{p12h} : 0.71 (90 percent CI 0.59 to 0.85)

Because the antacid lowers TPV levels, clinicians prescribing these drugs with TPV/RTV will have to consider the timing of the antacid dose.

These volunteers must have been glad when the study ended because all but one of them suffered some kind of gastrointestinal distress. During treatment with TPV/RTV alone, 17 (74 percent) had diarrhea, 11 (48 percent) had nausea, and nine (39 percent) had abdominal pain. Sixteen people (70 percent) reported some central nervous system complaint, including headache and loss of taste. All of these problems were mild, and no one quit the study because of them. There was only one clinically relevant lab abnormality, a grade 3 ALT gain.

This study also showed that single-dose TPV/RTV reduced hepatic CYP3A4 activity by 96 percent. Tipranavir induces CYP3A4 but clearly not nearly as much as 200 mg of RTV inhibits that drug-metabolizing enzyme.

Higher TMC114 tablet exposure with food

In a study of 50 people with plentiful PI experience and taking a failing PI regimen, TMC114/RTV doses of 300/100 or 600/100 twice daily or 900/100 mg once daily lowered median viral loads from 1.24 to 1.50 logs over eight

weeks.³⁰ In that period no one changed the nucleosides in their baseline regimen. At the Pharmacology Workshop, Richard Hoetelmans (Tibotec) offered food interaction findings on a new 400-mg solid formulation of TMC114 and an oral solution, both given with RTV [abstract 39].

The four-way crossover study design called for 16 healthy volunteers to take the tablet or oral solution with or without a standard breakfast. They also took 100 mg of RTV twice daily from two days before to one day after dosing of TMC114. One person withdrew consent during the washout after the first dosing period. Others

reported mild or moderate nausea, vomiting, dyspepsia, and headache.

Whereas food lowered exposure to TMC114 taken as an oral solution, food bumped up exposure to the tablet (Table 7).

Hoetelmans concluded that the TMC114 tablet formulation should be taken with food.

Table 7. Effect of food on TMC114 exposure

	Fasted	Fed	Change with food
<i>Oral solution</i>			
C_{max} (mean [CV] ng/mL)	5,571 (1,601)	3,701 (960)	33% decrease
AUC (mean [CV] ng • h/mL)	52,112 (15,923)	45,608 (14,400)	13% decrease
<i>Tablet</i>			
C_{max} (mean [CV] ng/mL)	2,769 (708)	3,614 (905)	35% increase
AUC (mean [CV] ng • h/mL)	32,452 (10,396)	43,938 (20,064)	42% increase

Two entry inhibitors and a nucleoside

Dose response effect of AMD070, a CXCR4 antagonist

A phase 1 study of AMD070, an orally bioavailable CXCR4 antagonist, showed a dose response effect, with most 12-hour concentrations of a 400-mg dose above the protein binding-adjusted 90 percent effective concentration (EC_{90}) of 125 nM. AMD070 has a 50 percent inhibitory concentration similar to that of its forerunner, AMD3100, which could not be taken orally (6.6 and 4.3 nM respectively against HIV-1 NL4.3 in MT-4 cells).

Nimalie Stone (Johns Hopkins University, Baltimore) charted AMD070 levels in healthy men taking single doses of 50, 100, 200, or 400 mg, twice-daily doses of 100 or 200 mg, and a single 400-mg dose with food [abstract 36]. Food had no impact on the drug's bioavailability.

The C_{max} and AUC proved dose-proportional across doses, though interindividual variation was wide. White blood cell gains, a possible marker of CXCR4 inhibition, ranged from 1.3- to 1.6-fold with the 50-mg dose and from 1.5- to 2.9-fold with 400 mg. AMD070 concentrations 12 hours after a single 400-mg dose ranged from 79 to 155 nM, though nearly everyone taking that dose had a concentration above the protein binding-adjusted EC_{90} . Multiple dosing did not result in drug accumulation. Some volunteers suffered mild and reversible headaches.



CYP3A4 inducers lower exposure of UK-427,857, a CCR5 antagonist

The CYP3A4 inducers rifampin and EFV lower levels of the CCR5 antagonist UK-427,857, reported Gary Muirhead (Pfizer Global Research and Development) [abstract 37]. Doubling the dose of UK-427,857 compensates for this inducing effect.

The placebo-controlled, parallel-group study involved 36 healthy men who took 100 mg of the CCR5 antagonist twice daily on study days 1 through 21. On days 8 through 21 they also took 600 mg of rifampin once daily, 600 mg of EFV once daily, or placebo. By comparing UK-427,857 troughs on days 7 and 17, the Pfizer team gauged the effect of the CYP3A4 inducers and adjusted the dose of the antagonist if necessary on days 22 through 28.

Muirhead calculated a 6.6-fold increase in CYP3A4 induction with rifampin and a 2.4-fold increase with EFV. Both drugs substantially lowered UK-427,857 exposure compared with placebo. By day 28 the dose adjustment had lifted exposure of the antagonist back to levels comparable with placebo (Table 8).

Elvucitabine, an NRTI with a difference

The sundry once-daily antiretroviral regimens now feasible make life easier for people starting down the road of lifelong therapy. Dare one anticipate *once-weekly* therapy? Pharmacology Workshop attendees got a glimmer of that hope in a review of the nucleoside cytosine analog elvucitabine by John Pottage (Achillion Pharmaceuticals) [abstract 38].

In vitro work indicated that elvucitabine has 5- to 10-fold greater antiviral activity than 3TC against wild-type HIV and HBV at respective 50 percent inhibitory concentrations of 4.8 and 1.0 nM. At doses of 50 mg or more daily, the nucleoside also slowed replication of 3TC-resistant M184V mutant virus. But those doses caused bone marrow toxicity.

Using data from studies of 29 healthy volunteers and 64 people with HBV infection, Pottage arrived at a “conservative” therapeutic window defined as a steady-state 24-hour AUC of 300 µg•h/mL and a C_{min} of at least 2 µg/L. To prevent bone marrow toxicity he calculated that the C_{min} must stay below 23 µg/L, which would keep peak concentrations under 40 µg/L in bone marrow.

With an estimated elimination half-life of 175 hours, elvucitabine could be a candidate for once-weekly therapy, and software-driven simulation settled on three once-weekly doses that yielded a C_{min}, C_{max}, and AUC within the therapeutic window—40, 50, and 75 mg. Other doses that fit the window were 5 mg twice daily; 5, 7.5, and 10 mg once daily; and 10, 15, and 20 mg every 48 hours.

DRUG-DRUG INTERACTIONS—GOOD, BAD, OR NEITHER

Antiretroviral drug-drug interactions can be good, or bad, or neither good nor bad. But they always take time to figure out and may require precise prescription planning, drug level monitoring, or dose adjustments. And, after all that, the person prescribed these drugs had better take them all and on time.

If only monotherapy had worked, things would be much simpler. And maybe it will yet, at least if you count an RTV-boosted PI as monotherapy. When the news arrived that some had started studying boosted PI monotherapy, Andrew Hill (Roche Laboratories) confessed he found the concept hard to swallow, since so many had choked on it the first time around. But in the Pharmacology Workshop’s first

review lecture—“MicroHAART”—Hill noted that boosted monotherapy has found its boosters.

Swiss clinicians studied IDV/RTV maintenance therapy after induction with IDV/RTV plus two nucleosides.³¹ Adjusting the IDV/RTV dose to keep IDV’s trough between 500 and 2,000 nM/L, these workers saw no consecutive rebounds above 400 copies/mL through 48 weeks. In the United States, clinicians looked at LPV/RTV as first-line therapy for 30 people at 400/100 mg twice daily for those weighing less than 70 kg and 533/133 mg twice daily for those weighing more.³² All but one reached a viral load below 400 copies/mL, but 50-copy results were not reported. Eight people dropped out of the study or added another drug by week 24. Hill added that early results of a solo SQV/RTV trial may appear this month at the XV International AIDS Conference in Bangkok.

But these are “early days” for recidivist monotherapists, Hill cautioned. Indeed, with once-daily double NRTIs like 3TC/ABC and TDF/FTC on the horizon, boosted-PI

Table 8. Dose adjustment compensates for low UK-427,857 levels with CYP3A4 inducers

	Geometric mean UK-427,857 concentration on day:		
	7	21*	28*
<i>Placebo</i>			
AUC (ng•h/mL)	550	624	580
C _{max} (ng/mL)	138	153	138
<i>EFV</i>			
AUC (ng•h/mL)	543	300 (49)	624 (110)
C _{max} (ng/mL)	140	68.1 (44)	163 (120)
<i>Rifampin</i>			
AUC (ng•h/mL)	695	256 (33)	723 (99)
C _{max} (ng/mL)	182	60.9 (30)	176 (97)

*Values in parentheses are percent ratios for day 21 or 28/day 7 compared with placebo.



monotherapy will have to prove highly safe and effective before its proponents can argue against adding a couple of nukes. In a stimulating talk reviewed at the end of this article, Hill himself called on colleagues to study lower doses of current combinations, after marshalling evidence that microHAART may sometimes prove feasible.

For at least the immediate future, though, clinicians and their pharmacologist allies will have to grapple with the interactions possible when they combine “drug X” with “drug Y,” with or without “drug Z.” And continued study of those interactions shows that continuing is a good idea, because early impressions can change—or at least come into question. A prime example of such shifts came in Pharmacology Workshop studies (reviewed in the second section of this article) challenging the conclusion that TDF consistently undercuts ATV. And a dozen studies discussed below affirmed that mixing antiretrovirals can often yield a productive match for reasons not always apparent *a priori*.

It’s hard enough for HIV pharmacology experts to keep up with all this, so what’s a harried clinician to do? Seek out a reliable pharmacologist, for starters, and a German group has just made that easier.

German drug-drug interaction hotline

Leonie Meemken (ifi-Institut, Hamburg) reported early experience with a ripe idea—a telephone/Internet hotline to answer questions about antiretroviral interactions and other pharmacologic issues [abstract 24]. Both physicians and pharmacists have tapped the hotline, which is managed by HIV pharmacologists. When necessary, questions get referred to clinical experts in other disciplines. Answers are returned within 24 hours.

So far about two thirds of the questions involve co-medications given with antiretrovirals, about one quarter involve only antiretrovirals, and the rest involve herbal agents. (In a Pharmacology Workshop study of 437 HIV-infected people in Barcelona, 25 percent reported using some complementary or alternative agent in 2003.³³) Co-medications have resulted in three quarters of reported toxic antiretroviral levels. Meemken gave hotline users high marks for their knowledge of antiretroviral pharmacology, but they often need help understanding the impact of other agents that they prescribe less often.

Hotline workers catalog questions and answers in a database that will be routinely analyzed. Groups in other countries who study and adapt this model to local needs

will render a valuable service to HIV clinicians and the people they treat.

Lopinavir and ritonavir

Separate studies surveyed the effect of LPV/RTV on CYP2C isoenzymes and its interactions with APV and EFV. Giving RTV with minidose cyclosporine A looks feasible in people who have liver transplants.

LPV/RTV boosts activity of CYP2C19 and CYP2C9

Drugs metabolized via CYP2C19, and possibly those metabolized via CYP2C9, may need their doses dialed upwards when given with LPV/RTV, which increases activity of both isoenzymes. Rosa Yeh (University of North Carolina, Chapel Hill) [abstract 13] reached that conclusion in a study inspired by earlier work showing drops in phenytoin, LPV, and RTV exposure when the three drugs are mixed.³⁴ Because CYP2C9 is the prime route of phenytoin metabolism and CYP2C19 a minor route, she rated activity of the two isoenzymes in 10 healthy volunteers given LPV/RTV.

Volunteers all weighed at least 50 kg and were within 20 percent of their ideal body weight. Their age averaged 26.8 years and ranged from 21 to 40 years. The study group

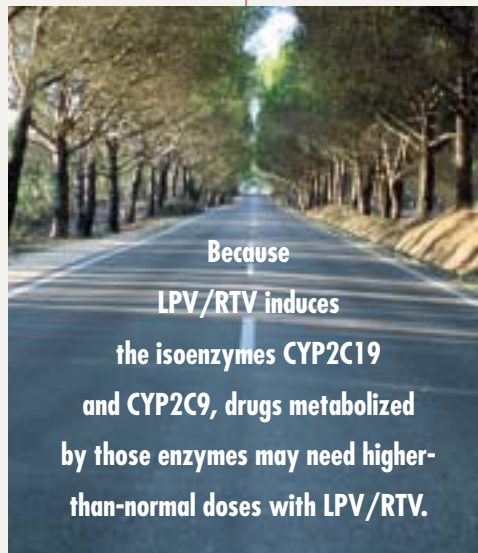
consisted of five African Americans and five Caucasians, seven men and three women. On study days 1 to 3 and 14 to 17, they took 10 mg of warfarin, a substrate for CYP2C9, and 40 mg of omeprazole, a substrate for CYP2C19. They took the standard twice-daily dose of LPV/RTV on days 4 to 17. The PIs significantly lowered exposure of both marker drugs, a result indicating increased activity of the two isoenzymes (Table 9).

Lopinavir and RTV concentrations stayed within the expected range. The study did not clarify how much LPV or RTV individually contributes to induction of CYP2C19 and CYP2C9.

Drugs metabolized by CYP2C19 include diazepam, phenytoin, omeprazole, propranolol, citalopram, imipramine, and certain barbiturates. Those metabolized by CYP2C9 include most nonsteroidal anti-inflammatories, S-warfarin, phenytoin, tolbutamide, and ibuprofen.

LPV moderates RTV boost of APV

A retrospective study by Marie-Claude Gagnieu (Edouard Herriot Hospital, France) found a significant





drop in elimination of APV when given with RTV or LPV/RTV [abstract 28]. But the ebb in elimination proved smaller with LPV/RTV than with RTV alone. The study involved three groups who had taken APV with or without LPV and RTV:

- APV alone at 1200 mg twice daily ($n = 41$)
- APV/RTV at 600/100 mg twice daily ($n = 29$)
- APV/LPV/RTV at 600/400/100 mg twice daily ($n = 35$)

The elimination rate constant measured $0.31 \pm 0.14/h$ with APV alone, $0.17 \pm 0.08/h$ with LPV/RTV, and $0.116 \pm 0.137/h$ with RTV. In line with these findings, APV C_{mins} were significantly lower with APV alone (0.59 ± 0.77 mg/L) than with LPV/RTV (0.99 ± 0.54 mg/L, $P = 0.01$) or just RTV (1.65 ± 0.74 mg/L, $P = 0.001$).

Interindividual variability in APV elimination proved less with LPV/RTV than only with RTV, but concentrations of LPV and RTV did not correlate with elimination of the third PI.

Interactions between RTV and cyclosporine A after liver transplant

Martin Vogel (University of Bonn) had to cut the standard dose of cyclosporine A drastically in three HIV-infected liver transplant patients restarting LPV/RTV [abstract 19]. But the three have not had an acute or chronic rejection 311, 504, and 720 days after the transplant.

Vogel recorded 12-hour PK profiles of cyclosporine A before and after these people restarted treatment with two nucleosides and LPV/RTV. After antiretroviral therapy resumed, elimination half-lives of cyclosporine A rose as high as 38 hours. To return to cyclosporine AUCs equivalent to those seen before PI therapy started again, daily doses of the anti-rejection drug had to be sliced to a range of 5 percent to 20 percent of the original dose. Because of flat cyclosporine A absorption/elimination profiles, Vogel could reliably monitor the drug's level by measuring troughs.

Journal of Negative Results

One can leave a Pharmacology Workshop with the strong impression that almost everything but earlobe length tweaks drug levels up or down. But that's just because results are much more interesting when they show something

unexpected, or something dangerous, or something salutary—so those are the data that get presented and published. But just as often drugs don't interact, genes don't disrupt drug distribution, and gender doesn't mean a thing (pharmacokinetically speaking).

Authors of studies with such equable outcomes have a harder time getting published, unless they submit to *The Journal of Negative Results (JNR)*, an august chronicle imagined by David Burger of the University Medical Center, Nijmegen. He nominated his own work on CYP2B6 genotype and EFV [abstract 54] for *JNR*, and two other Pharmacology Workshop studies on PIs and EFV easily qualify.

(Some) CYP2B6 shifts do not explain EFV variability

Because EFV levels vary greatly from person to person, proving toxic in some, researchers are trying to track down triggers of that variability. Earlier this year, AIDS Clinical Trials Group (ACTG) investigators found that a TT genotype at position 516 of the gene that codes for

CYP2B6—the isoenzyme engine of EFV metabolism—turned up in 20 percent of blacks and 3 percent of whites.³ The TT genotype also correlated with slower clearance and high levels of EFV, and with more side effects.

Burger found an easier-to-identify predictor of high EFV exposure and more side effects—female gender.³⁵ And that correlation held true independently of body weight. Pursuing this research goal, Burger turned from gender to genetics, hypothesizing that a mutation labeled CYP2B6*5—already linked to poor metabolism of EFV—could drive up drug levels [abstract 54].

Burger analyzed samples from people taking EFV who used his lab's TDM service in 2002 and 2003. Of 228 individuals with TDM samples, 189 (82.9 percent) had a wild-type CC genotype, 33 (14.5 percent) had the heterozygote CT variant, and 6 (2.6 percent) had the homozygote TT variant. Defining a toxic EFV level as greater than 4 mg/L, Burger found no gene-based difference in proportions with a toxic concentration ($P = 0.591$):

- CC: 19.6 percent
- CT: 12.1 percent
- TT: 16.7 percent

Table 9. Effect of LPV/RTV on CYP2C19 and CYP2C9

	Day 1 (before LPV/RTV)	Day 14 (with LPV/RTV)	GMR D14/D1 (95% CI)	P	Change in 2C19 activity
Omeprazole metabolic ratio	1.28	0.41	0.32 (0.21 to 0.49)	0.001	68% increase
	Day 1 (before LPV/RTV)	Day 14 (with LPV/RTV)	GMR D14/D1 (95% CI)	P	Change in 2C9 activity
S-Warfarin AUC ($\mu\text{g} \cdot \text{h/mL}$)	12.76	9.52	0.75 (0.64 to 0.86)	0.002	25% increase

AUC = area under the concentration-time curve; GMR = geometric mean ratio.



The analysis did disclose a significantly greater mutation rate (CT plus TT) in Caucasians (21.6 percent) than in blacks (8.2 percent) or Asians (0 percent) ($P = 0.036$)—a reversal of the mutation prevalence found in the ACTG study of another position on the gene coding for CYP2B6.³

Current PIs do not affect EFV concentrations

A retrospective study of EFV levels by Jean-Marie Poirier (Saint-Antoine University Hospital, Paris) found that taking a PI with the nonnucleoside did not significantly affect EFV exposure [abstract 25]. The analysis involved 33 people taking EFV alone and 145 taking the standard dose of EFV plus NFV or an RTV-boosted PI. Everyone was also taking two nucleosides. Comparing EFV levels measured at least eight hours after dosing, Poirier discerned no differences between the PI and non-PI groups in percentages with high, low, or therapeutic range EFV quotients (Table 10).

Efavirenz levels proved marginally but not significantly higher with certain PIs than with EFV alone (mean \pm standard deviation [SD]):

- EFV alone ($n = 33$): $2,960 \pm 1,601$ ng/mL
- Plus APV/RTV(600/100 mg twice daily) ($n = 15$): $2,960 \pm 1,601$ ng/mL
- Plus IDV/RTV(600 or 800/100 mg twice daily) ($n = 22$): $3,313 \pm 1,212$ ng/mL
- Plus LPV/RTV (400/100 or 533/133 mg twice daily) ($n = 48$): $3,318 \pm 2,485$ ng/mL
- Plus NFV (1,000 or 1,250 mg twice daily) ($n = 12$): $3,452 \pm 1,830$ ng/mL
- Plus SQV/RTV(800 or 1,000/100 mg twice daily) ($n = 15$): $4,000 \pm 2,342$ ng/mL

Steady LPV and IDV troughs with combination

Lopinavir and IDV troughs in five people taking the PIs with RTV did not differ significantly from troughs of two reference populations taking LPV/RTV (400/100 mg twice daily) or IDV/RTV (400/100 mg twice daily). Saint-Antoine University Hospital's Jean-Marie Poirier did find significantly lower RTV troughs with LPV/RTV than with IDV/RTV or LPV/RTV/IDV [abstract 32].

The five retrospectively studied people were all taking 400 mg of LPV and IDV twice daily plus 100 mg of RTV twice daily and two nucleosides. Poirier measured troughs from samples collected 10 to 14 hours after dosing. The reference populations consisted of 106 people taking IDV/RTV and 185 taking LPV/RTV.

Mean (\pm SD) LPV and IDV troughs were equivalent from group to group:

- LPV: $6,173 \pm 1,002$ ng/mL with LPV/RTV/IDV and $6,253 \pm 4,124$ ng/mL with LPV/RTV
- IDV: 625 ± 180 ng/mL with LPV/RTV/IDV and 561 ± 400 ng/mL with IDV/RTV

Mean (\pm SD) RTV troughs measured 217 ± 171 ng/mL with LPV/RTV ($P < 0.02$ versus both other groups), 398 ± 159 ng/mL with LPV/RTV/IDV, and 576 ± 499 ng/mL with IDV/RTV.

Table 10. **EFV concentrations with or without a PI**

	>4,000 ng/mL	1,000 to 4,000 ng/mL	<1,000 ng/mL
Without PI (% patients)	21	70	9
With PI (% patients)	28	70	4

Fruitful teamings, novel tactics, triple PIs

Several groups reported good results—often with novel tactics—in studies of RTV-boosted PIs. And all but one of these studies involved the prototype PI, SQV. Two of the SQV trials paired it with other PIs plus RTV. The outlier study in this cluster sized up fosamprenavir (FPV)/RTV for people with well-aged PI histories.

Once-daily FPV/RTV after PI failure

People with six protease mutations had less than a 1-log drop in viral load after one month of once-daily FPV/RTV (1,400/200 mg), reported Anne-Marie Taburet (Kremlin Bicêtre Hospital, Paris) [abstract 15]. People with two baseline protease mutations all shaved more than 2 logs off their viral load at one month. But the one-month response did not correlate with number of baseline mutations in people who had three, four, or five.

The ongoing study involves 26 men and 12 women with two or more APV or RTV mutations after failure of one or more PI regimens. The average number of PIs taken stood at three (range one to seven), while the median starting viral load measured 4.44 logs (range 3.03 to 5.67 logs) and the median CD4 count 228 cells/mm³ (range 18 to 503 cells/mm³). Twelve study participants also took a nonnucleoside, and five of them added another 100 mg of RTV. By treatment month 6, two people had quit because of gastrointestinal complaints, and two had a grade 3 or 4 triglyceride jump.

In a one-month analysis of 33 people, all three with only two baseline protease mutations had more than a 2-log drop in viral load, and all three with six mutations had less than a 1-log decline. Among 26 people with three, four, or five baseline protease mutations, 16 had less than a 1-log viral load drop at month 1 and 10 lost 2 logs or more, a nonsignificant difference. Viral load declines did not correlate with an inhibitory quotient measured as unbound APV/90 percent inhibitory concentration.



Among people with four or fewer baseline protease mutations and an amprenavir trough above 1,000 ng/mL, the median viral load drop measured 1.1 log at month 3. But that median had crept up to a 0.7-log decline by month 6. Median troughs stood well above 1,000 ng/mL at months 1, 3, and 6, but troughs ranged widely:

- Month 1 ($n = 35$): 1,736 (219 to 9,777) ng/mL
- Month 3 ($n = 34$): 2,103 (64 to 13,035) ng/mL
- Month 6 ($n = 33$): 2,057 (<40 to 6,069) ng/mL

SQV/RTV and rifampin for HIV and TB

Once-daily soft-gel SQV/RTV (1,600/100 mg) did not alter levels of rifampin or isoniazid in 31 people coinfecting with HIV and *Mycobacterium tuberculosis*. Carlos Azuaje (Hospital Universitari Vall d'Hebron, Barcelona) reported that rifampin did lower SQV and RTV exposure [abstract 14]. Although those decreases lacked statistical significance, 10 people wound up with SQV C_{\min} s below 0.05 $\mu\text{g/mL}$, and five of them had a virologic failure.

The 26 men and five women studied began TB therapy before starting antiretrovirals, which they had never used before. The regimen consisted of 600 mg of rifampin daily for nine months, 300 mg of isoniazid daily for nine months, 30 mg/kg of pyrazinamide daily for two months, with or without 25 mg/kg of ethambutol daily for two months. When people stopped pyrazinamide and ethambutol, they started a once-a-day regimen of SQV/RTV (1,600/100 mg), enteric-coated dDI (400 or 250 mg depending on weight), and 300 mg of 3TC.

Two people had to stop the PIs because of 5-fold transaminase leaps; both had HCV infection. Fifteen others also had HCV infection, and three had HBV infection.

The AUC, C_{\max} , and C_{\min} of rifampin and isoniazid did not change when people started taking antiretrovirals. But levels of SQV and RTV proved nonsignificantly lower with tuberculosis therapy than afterwards (Table 11).

Although five of 10 people with SQV troughs below 0.05 $\mu\text{g/mL}$ during TB therapy endured a virologic failure, 64 percent of the group reached a viral load below 50 copies/mL by month 12, while the median CD4 count climbed from 169 cells/mm³ at baseline to nearly 300 cells/mm³ at month 12. The TB regimen cured all study participants.

Azuaje and colleagues are now testing 1,000/100 mg of SQV/RTV twice daily in people taking rifampin for TB.

SQV/RTV with ATV or FPV

Atazanavir and FPV qualify as attractive partners for RTV-boosted SQV, explained Marta Boffito (Chelsea and Westminster Hospital, London), because the primary resistance profiles of the first two PIs differ from that of SQV [abstract 17]. Also, APV and SQV proved synergistic *in vitro*, and ATV/SQV can be taken once daily.

Boffito studied the two boosted double PIs in 36 people (18 for each combination) responding well to SQV/RTV. Everyone not already taking SQV HGC switched to that formulation, at an RTV-boosted dose of 1,600/100 mg once daily in the ATV group and 1,000/100 mg twice

daily in the FPV group. After steady-state SQV readings on study day 1, the ATV group added 300 mg of that PI once daily and the FPV group added 700 mg twice daily. On day 12, the FPV group doubled their RTV heft to 200 mg twice daily. Steady-state measurements of the double boosted PIs came on day 11 in both groups and also on day 22 in the FPV group.

Adding ATV to 1,600/100 mg of SQV/RTV boosted SQV's trough by 112 percent, peak by 42 percent, 0- to 24-hour AUC by 60 percent, and elimination half-life by 17 percent.

The first three changes were statistically significant. Ritonavir's peak rose 34 percent with ATV and its 0- to 12-hour AUC 41 percent, both significant changes. Atazanavir levels proved comparable to those in earlier studies of people taking ATV/RTV without SQV. Seven of 18 people had SQV troughs above the target 100 ng/mL with SQV/RTV; 16 of 18 crossed that threshold after starting ATV.

Total and unconjugated bilirubin rose 6-fold during co-administration of ATV and coasted back to baseline values when people stopped that PI. Four people with hyperbilirubinemia had scleral icterus and two had jaundice. A few people also reported mild to moderate abdominal pain, diarrhea, skin rash, headache, and fatigue during double-PI therapy.

Boffito observed that the reason for higher SQV levels with ATV "is not entirely clear" because earlier work suggested the mechanism is not inhibition of CYP isoenzymes. Further study of this combination with lower doses of ATV seem warranted, she added, to see if less ATV can boost SQV while promoting fewer side effects.

When people added FPV to 1,000/100 mg of SQV/RTV twice daily, SQV concentrations fell nonsignificantly. Upping the RTV dose to 200 mg twice

Table 11. Lower SQV/RTV exposure with rifampin/isoniazid

	Without TB therapy	With TB therapy	% decrease
SQV			
AUC _{0-24h} ($\mu\text{g/mL}\cdot\text{h}$)	22.9	12.2	32
C_{\max} ($\mu\text{g/mL}$)	3.3	2.0	35
C_{\min} ($\mu\text{g/mL}$)	0.14	0.06	46
RTV			
AUC _{0-24h} ($\mu\text{g/mL}\cdot\text{h}$)	14.4	9.9	42
C_{\max} ($\mu\text{g/mL}$)	2.0	1.2	49
C_{\min} ($\mu\text{g/mL}$)	0.14	<0.05	64



daily reversed those dips and yielded non-significant gains in SQV exposure compared with baseline levels. A 54 percent drop in RTV's trough with the addition of FPV may explain the dwindling SQV quotients. Everyone in this group had an SQV trough above the 100-ng/mL threshold with or without FPV. Mild to moderate fatigue slowed three people, nausea affected two, and diarrhea one.

LPV/RTV with three doses of SQV

Measuring SQV HGC levels in people adding 400 mg, then 600 mg, then 800 mg twice daily to standard-dose LPV/RTV, Richard Bertz (Abbott Laboratories) found that the 600- and 800-mg doses yielded troughs equivalent to those in earlier studies of 1,000/100 mg of SQV/RTV twice daily [abstract 18].

The study involved 12 anti-retroviral-naïve men with detectable viral loads who started standard doses of LPV/RTV plus AZT and 3TC. After one week they added 400 mg of SQV HGC twice daily. A week later they raised that to 600 mg twice daily, and a week after that to 800 mg twice daily. Saquinavir concentrations proved equivalent with the 600- and 800-mg doses but significantly lower with 400 mg (Table 12).

Saquinavir concentrations with 600 or 800 mg twice daily measured up to those with 1,000/100 mg of SQV/RTV twice daily, and (except for a lower trough) to those with 800 mg of SQV soft gel twice daily plus LPV/RTV in healthy volunteers. Saquinavir did not affect levels of LPV or RTV in this study.

SQV in two nucleoside-sparing regimens

Nucleoside-sparing regimens continue to draw research interest as multi-NRTI-resistant virus gains sway and people succumb to nucleoside toxicities. The Pharmacology Workshop saw reports of two no-nuke studies, one combining boosted SQV with EFV and one relying on two boosted PIs.

Because EFV induces CYP3A4, it can cut SQV levels, noted Reshma Autar (HIV-NAT, Bangkok) [abstract 21]. But studies show that RTV boosting moderates that effect.^{36,37} The HIV-NAT team measured SQV and EFV in seven men and four women—all Thais—at weeks 2, 4, 8, 12, and 24 of treatment with 1,000/200 mg of SQV/RTV twice daily plus standard once-daily EFV. Study participants had a median weight of 64 kg (interquartile range [IQR] 50 to 70 kg), a median body mass index of 22.5 kg/m² (IQR 19.5 to 25.7 kg/m²), a median CD4 count of 345 cells/mm³ (IQR 235 to 408

cells/mm³), and a median viral load of 4.4 logs (IQR 3.8 to 4.7 logs).

Drug levels measured 12 hours after dosing showed non-significant drops in median SQV troughs and a significant rise in EFV mid-dose level at week 12 but not at week 24. A few people had SQV troughs below a threshold of 0.1 mg/L at weeks 8, 12, and 24 (Table 13).

The waning SQV troughs may mean EFV does not exert its full CYP3A4-inducing effect by week 2, Autar speculated.

Eight people (73 percent) reached a viral load below 50 copies/mL by week 24. The median viral load fell 2.7 logs in that time (IQR -3.0 to -2.1), while the median CD4 count rose 95 cells/mm³ (IQR -73 to +129 cells/mm³).

Mild to moderate side effects did not require dose reductions or treatment breaks. Grade 4 liver toxicity emerged in one person, who lowered the EFV dose to 400 mg daily and the RTV dose to 100 mg twice daily. Another person trimmed the EFV dose to 400 mg daily and the SQV dose to 1,600 mg daily. Concentrations measured after dose reductions were not included in this analysis.

In the LOPSAQ study, Schlomo Staszewski (J.W. Goethe University, Frankfurt) counted 77 virologic responders among 126 people who switched from a failing nucleoside-backbone regimen to standard-dose LPV/RTV plus 1,000 mg of SQV twice daily [abstract 47]. He defined responders as those with a baseline viral load below 100,000 copies/mL who reached a load below 400 copies/mL and those with a baseline load above 100,000 copies/mL who went below 10,000 copies/mL. Earlier analysis determined that non-responders had lower CD4 counts, higher viral loads, and more resistance when they started the three-PI regimen. At the Pharmacology Workshop, Staszewski showed that PI concentrations also foretold failure.

The PK comparison involved 36 responders and 20 non-responders who had drug levels measured after taking the PI-only regimen for at least 14 days. Saquinavir AUC, C_{min}, and C_{max} all proved significantly lower in the non-responders ($P = 0.02$, $P = 0.01$, and $P = 0.05$), as did LPV C_{min} ($P = 0.05$) and RTV C_{min} ($P < 0.001$). The median RTV trough measured 129 ng/mL (range 29 to 633 ng/mL) in responders and 60 ng/mL (range 22 to 377 ng/mL) in nonresponders. Median SQV troughs stood at 592 ng/mL (range 47 to 2,940 ng/mL) in responders and 287 ng/mL (range 120 to 1,720 ng/mL) in nonresponders. Respective LPV troughs were 3,605

Table 12. Mean SQV levels (± SD) at three doses with LPV/RTV

	400 mg bid	600 mg bid	800 mg bid
C _{max} (µg/mL)	1.22 ± 0.55*	2.44 ± 1.40	2.44 ± 0.85
C _{min} (µg/mL)	0.26 ± 0.16*	0.51 ± 0.28	0.60 ± 0.33
C _{trough} (µg/mL)	0.45 ± 0.25*	0.92 ± 0.57	1.06 ± 0.52
AUC _{12h} (µg•h/mL)	7.64 ± 2.43*	15.6 ± 7.43	17.5 ± 7.13
IQ (C _{trough} /IC ₅₀)	1.41	3.37	3.71

* $P < 0.05$ versus 800 mg bid.
bid = twice daily; IC₅₀ = 50% inhibitory concentration; IQ = inhibitory quotient.



ng/mL (range 812 to 9,970 ng/mL) and 2,570 ng/mL (range 720 to 11,300 ng/mL).

RTV once daily to boost SQV twice daily?

The standard boosting dose of RTV stands at 100 mg once or twice daily, but several studies³⁸⁻⁴² suggested to Andrew Lubber (Tower Infectious Diseases, Los Angeles) that a lower dose may do as well with some PIs [abstract 16]. To test that hypothesis, he recruited six men, three of them naive to antiretrovirals and three who had not touched antiretrovirals for two to six years. They all took SQV HGC 1,600 mg with RTV 100 mg, both once daily for 14 days. On day 15 they took their 1,600/100-mg morning dose, then came to the clinic and 12 hours later swallowed another 1,600 mg of SQV without RTV.

Comparing boosted SQV levels on day 14 and after the unboosted SQV dose on day 15, Lubber found a 28 percent *higher* 12-hour AUC after the unboosted dose. Meanwhile, RTV's AUC during day 15 sampling measured 32 percent of its AUC during day 14 sampling.

Lubber concluded that 100 mg of RTV can boost a second SQV dose taken 12 hours later, even though RTV levels drop sharply over that half day. That makes sense, he proposed, because RTV inhibits CYP3A4 in the liver and/or gut, not in the blood where it's usually measured. He cautioned that this pilot study of only six people showed wide interpatient variability, that the second SQV dose on day 15 was not given at steady state, and that food was not controlled for at dosing. Lubber has mounted a similar study in 20 people.

How much drug gets inside cells?

Andrew Lubber's suggestion that RTV remains active at the cellular level after its blood levels wane flags the importance of measuring antiretrovirals in cells. When plasma levels parallel cell levels, noted Sara Colombo (University Hospital, Lausanne), traditional blood-based TDM probably gets the job done [abstract 52]. But when drug levels don't correlate in plasma and cells, "there might be room for TDM improvement using either direct intracellular determinations or indirect corrections of plasma concentrations,

possibly based on predictive factors (genotypes of transporters or binding proteins), which remain to be developed." In other words, TDM could get a lot more complicated, but also a lot more precise. Colombo and the University of Liverpool group cracked open the door to this future.

Differing intracellular and plasma ratios of PIs and NNRTIs

In a multicenter study, Colombo measured 669 plasma concentrations and 178 concentrations in PBMCs from people taking PIs or the NNRTIs NVP and EFV. Then she figured intracellular-to-extracellular ratios and plotted log-transformed intracellular-to-extracellular relations for each drug taken.

Saquinavir, followed by NFV and IDV, had the best intracellular-to-extracellular ratios among PIs, while EFV easily outdid NVP by this measure (Table 14).

The reason for NVP's poor accumulation remains unknown. Possibilities, Colombo suggested, include active ejection and intracellular metabolism.

Colombo traced strong correlations between plasma and cell-associated concentrations of NFV ($r = 0.85$, slope = 0.93, $P < 0.0001$) and SQV ($r = 0.8$, slope = 0.76, $P = 0.0002$). Because she had limited data on LPV and NVP, their correlation plots are more tenuous, but Colombo believes plasma and cell-associated concentrations of LPV probably correlate well ($r = 0.6$, slope = 0.87, $P = 0.006$) while there appears to be no correlation for NVP ($r = 0.1$, slope = -0.3, $P = 0.8$). Plasma and cell-associated levels of EFV correlated weakly ($r = 0.6$, slope = 0.69, $P < 0.0001$).

Colombo concluded that plasma TDM of NFV, SQV, and probably LPV offers a good correlate for cell-associated drug sums. But standard TDM of EFV and NVP is more iffy because plasma concentrations of those drugs "poorly reflect" cell-associated stockpiles.

PIs in CD4 and CD8 cells

Most readers need no reminding that results such as Colombo's and those from a related study by Jennifer Ford (University of Liverpool) cannot be taken as gospel because variables ranging from sample size to assay

Table 13. Median SQV troughs and mid-dose EFV levels in an NRTI-free regimen

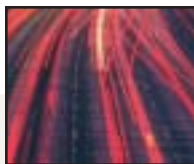
	Week 2	Week 4	Week 8	Week 12	Week 24
SQV					
C_{min} (mg/L)	1.07	0.62	0.84	0.26*	0.35†
IQR (mg/L)	0.62 to 1.73	0.37 to 1.30	0.30 to 1.69	0.11 to 2.19	0.18 to 0.89
n (%) <0.1 mg/L	0	0	1 (9.1)	2 (18.2)	1 (10)
EFV					
C_{12h} (mg/L)	3.21	3.43	4.05	5.06‡	2.28
IQR (mg/L)	2.20 to 7.08	2.53 to 5.18	2.65 to 8.75	3.22 to 9.00	1.67 to 5.64
n (%) <1.0 mg/L	0	0	0	0	0

C_{12h} = concentration at 12 hours; IQR = interquartile range.

* $P = 0.328$ versus week 2.

† $P = 0.093$ versus week 2.

‡ $P = 0.013$ versus week 2.



accuracy affect the data derived [abstract 51]. So it should surprise no one that some results may differ from one study to the next. Whereas IDV came in second in Colombo's charting of intracellular-to-extracellular accumulation, it came in last in Ford's analysis, trailing NFV, SQV, RTV, and LPV.

Ford reported findings from two studies—the first involving levels of SQV and RTV in 12 people taking those PIs at a dose of 1,600/100 mg once daily, and the second involving levels of five PIs in CD4 and CD8 cells sorted from PBMCs. The *in vivo* study found cell-associated-to-plasma ratios of 3.31 for SQV and 1.46 for RTV—not terribly far from the mean ratios Colombo found in slightly larger patient groups. Measuring expression of the drug transporter P-glycoprotein (P-gp) on lymphocytes, Ford traced no link between P-gp expression and SQV or RTV accumulation in cells.

In the *in vitro* study Ford spiked total lymphocytes and CD4 and CD8 subsets with 10 μ M of IDV, LPV, NFV, RTV, and SQV for two hours. Gauging intracellular-to-extracellular ratios in this experiment, she arrived at a ranking that held true for total T cells, CD4s, and CD8s:

$$\text{NFV} > \text{SQV} > \text{RTV} = \text{LPV} > \text{IDV}$$

Accumulation of RTV, LPV, IDV, and NFV proved significantly higher in CD4 cells than in CD8 cells. Again Ford discerned no link between P-gp expression and PI accumulation, except for lower SQV accumulation in CD8s expressing more P-gp ($r^2 = 0.34$, $P = 0.048$).

Why did Colombo rate IDV a good cell-associated accumulator while Ford ranked it last? An obvious difference between their studies is that Ford started with PBMCs isolated from 12 buffy coats, while Colombo looked at drug levels in PBMCs from people. And her sample of IDV takers numbered only three (Table 14).

Ford observed that her *in vitro* drug accumulation ranking does reflect the relative lipophilicity of the PIs she studied, a connection that suggests passive diffusion plays an important role in how much PI gets into the cell. But, she added, passive diffusion may not be the only player, a possibility suggested by the significantly higher PI accumulation in CD4s than in CD8s.

As for P-gp, Ford suggested that the correlation between its expression on CD8—but not CD4—cells and SQV levels may reflect higher P-gp expression on CD8s than

on CD4s. But she pointed to “an apparent disconnect” between this *in vitro* finding and what goes on in people since she found no tie between SQV exposure and total PBMC P-gp *in vivo*.

For now, the ultimate question for clinicians is how much they should start worrying about how much drug gets into which cells. Johns Hopkins University's Charles Flexner counseled calm for people using TDM, noting that study after study has linked plasma levels to response.

When is less enough?

And besides, it just may be that some antiretroviral doses

used today are higher than they have to be. That provocative proposal came from Roche Laboratories' Andrew Hill in the Pharmacology Workshop's first talk—which he titled “MicroHAART.” Hill did not suggest clinicians should start cutting doses tomorrow, but he marshaled

evidence suggesting that the concept deserves scrutiny.

Numerous studies show that more people quit or switch antiretrovirals because of toxicity than because of virologic failure, Hill reminded colleagues. In the Italian ICONA cohort of people starting antiretrovirals, toxicity explained 50 percent of failures and poor adherence another 20 percent.⁴³ Lower, more tolerable doses may improve adherence and thereby enhance long-term efficacy. So why not shoot for these drugs' minimum effective dose rather than their maximum tolerable dose?

Hill reeled off a list of eight studies that found no greater benefit with four-drug regimens than with the archetypal three. Indeed, these studies sometimes disclosed trends toward more failures with four drugs, trends not entirely explained by greater toxicity. Hill maintained that no quad therapy has outdone two nucleosides plus EFV or a boosted PI in lowering viral loads.

Pilot studies or cohort analyses suggest that some antiretrovirals—by no means all—work as well or yield adequate concentrations at doses lower than now used:

- Two studies charted equivalent responses to 30 and 40 mg of d4T.^{44,45}
- AZT, licensed at 1,600 mg daily and now given at 600 mg, may work as well at 400 mg.⁴⁶
- Indinavir has proved effective at an RTV-boosted dose of 400/100 mg twice daily.⁴⁷

Table 14. Mean intracellular-to-extracellular ratios for PIs and NNRTIs

	PIs						NNRTIs	
	SQV	IDV	NFV	RTV	LPV	APV	EFV	NVP
Mean	4.94	2.87	2.71	0.94	0.65	0.36	0.90	0.14
Standard error	0.71	0.75	0.21	0.18	0.12	0.15	0.08	0.07
n	16	3	40	16	16	4	62	11



- Ritonavir-boosted APV stymied HIV as well at 50 mg as at 100 mg twice daily, and as well at 100 mg as at 200 mg once daily.³⁸
- Lopinavir/RTV corralled virus equally well at 200/100 mg and 400/200 mg twice daily.⁴⁸
- Efavirenz doses lower than 600 mg daily seemed effective in an early clinical trial.⁴⁹

Hill noted that lower doses of ddI, ABC, TDF, and NFV have not proved effective. He cautioned that lower-dose strategies may not work for people who already have resistant virus, and he advised against induction-maintenance approaches that use two or three nucleosides or an unboosted PI.

Lower doses may lower the threshold to resistance, Hill allowed. But high doses can also promote resistance by causing side effects and breeding faulty adherence. He estimated that a two-year trial involving 600 treatment-naive people would be needed to see if certain lower-dose combinations work.

Some attendees voiced reluctance over translating data like those Hill cited into a rationale for clinical trials. Andrea De Luca (Catholic University of the Sacred Heart, Rome) suggested such findings may not justify trials, but perhaps support TDM to see if doses can be lowered in some individuals. And Hill himself wondered how anxious pharmaceutical companies would be to support trials to trim doses—and perhaps profits. But one can imagine long lines of trial volunteers. ■

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Honoring Our Heroes 2004



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ABSTRACTS

Journal of Infectious Diseases

Mutations in HIV-1 reverse transcriptase potentially associated with hypersusceptibility to nonnucleoside reverse transcriptase inhibitors: Effect on response to efavirenz-based therapy in an urban observational cohort

Tozzi V, Zaccarelli M, Narciso P, et al

BACKGROUND: Hypersusceptibility to nonnucleoside reverse transcriptase inhibitors (NNRTIs) was described in association with reverse transcriptase (RT) mutations conferring resistance to nucleoside reverse transcriptase inhibitors (NRTIs). We evaluated the effect of RT mutations associated with hypersusceptibility to NNRTIs on the response to efavirenz-based therapy. **METHODS:** We analyzed an observational database of patients for whom highly active antiretroviral therapy failed and who received genotypic resistance testing-guided therapy, either efavirenz- or protease inhibitor (PI)-based. Study endpoints were achievement of virus load <80 copies/mL, achievement of virus load <80 copies/mL without rebound to >500 copies/mL, and changes in CD4 cell counts. **RESULTS:** The baseline RT mutations M41L, M184V, L210W, and T215Y and the M41L/T215Y and M41L/T215Y/M184V combinations were associated with virological suppression for efavirenz-treated patients, whereas, for PI-treated patients, only the M184V mutation was associated with virological suppression, and the L210W mutation showed a negative correlation; no correlation was found between any mutation and virological response without rebound. **CONCLUSIONS:** The M41L, M184V, L210W, and T215Y mutations were associated with a better, although transient, virological outcome in patients treated with efavirenz-based regimens.

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Journal of Acquired Immune Deficiency Syndromes

Changes in total lymphocyte count as a surrogate for changes in CD4 count following initiation of HAART: Implications for monitoring in resource-limited settings

Mahajan AP, Hogan JW, Snyder B, et al

BACKGROUND: A major obstacle to the administration of highly active antiretroviral therapy (HAART) in resource-limited settings is the high cost of CD4 count testing. The total lymphocyte count (TLC) has been proposed as a surrogate marker to monitor immune response to therapy. **OBJECTIVE:** To assess, in a developed country setting, the capability and clinical utility of TLC change as a surrogate marker for CD4 count change in monitoring patients on HAART. **METHODS:** Longitudinal co-variation between changes in TLC and concomitant changes in CD4 count following the initiation of HAART was examined using a retrospective cohort study of 126 HIV-positive patients attending The Miriam Hospital at Brown University in Providence, Rhode

Island. Analyses included evaluation of the direction of TLC change as a marker for direction of CD4 change, using sensitivity and specificity; evaluation of absolute change in TLC as a marker for benchmark changes in CD4 (≥ 50 over six months, ≥ 100 over 12 months), using receiver-operator characteristic (ROC) curves; and a regression model of change in TLC as a function of change in CD4, to understand within-individual variation of longitudinal TLC measures. **RESULTS:** In the first 24 months of HAART, the sensitivity of a TLC increase as a marker for CD4 count increase over the same time period ranged from 86-94 percent, and the specificity ranged from 80-85 percent. The median change in TLC among patients with a CD4 count rise of ≥ 100 cells/mm³ at one year of HAART was +766 cells/mm³ while that of patients with a CD4 count rise of <100 cells/mm³ was +100 cells/mm³. The area under the corresponding ROC curve was 0.89, suggesting that change in TLC discriminates well between those with one-year CD4 change of ≥ 100 versus those with change < 100 . From a regression analysis, we found that mean change in TLC per 1 cell/mm³ change in CD4 count was 7.3 (SE 1.2, $P < 0.001$). The degree of this association varied from individual to individual but was positive for all individuals. **CONCLUSIONS:** Within the first two years of HAART, the direction of change in TLC appears to be a strong marker for direction of concomitant change in CD4 count (sensitivity 86-94 percent and specificity 80-85 percent, depending on length of interval). Positive and negative predictive values depend on the proportion of CD4 changes that are positive. In this cohort, that proportion is 87.9 percent, which yields high positive predictive value (96-98 percent) but lower negative predictive value (43-63 percent). Findings from the regression model suggest that taking multiple measurements of TLC at more frequent intervals may reduce variability and potentially improve predictive accuracy.

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Oral Diseases

Oral manifestations of HIV infection in relation to clinical and CD4 immunological status in northern and southern Thai patients

Kerdpon D, Pongsirivet S, Pangsomboon K, et al

OBJECTIVES: To assess prevalence and variations in the oral manifestations of HIV in HIV-infected subjects in southern Thailand (a new HIV epidemic) and northern Thailand (a mature epidemic), and the association with age, sex, risk behaviors, CD4 count, and medication used. **SUBJECTS AND METHODS:** A total of 102 and 135 HIV-infected individuals were enrolled in northern and southern hospitals, respectively. Oral and hematological examination was performed after sociodemographic interview of the patients. Clinical history was retrieved from patients' medical records. **RESULTS:** Oral candidiasis (OC, 55 percent), oral hairy leukoplakia (OHL, 21 percent), and HIV-associated periodontal disease (14 percent) were among the most common oral lesions in

southern Thailand. OHL (38 percent), OC (25 percent), and HIV-associated periodontal disease (15 percent) were the three most common lesions in the north. A significant association was found between any oral lesion, OC, particularly the pseudomembranous type (PC), and CD4 <200 cells/mm³ at both sites. A negative relationship was found between systemic antifungal treatment and OC including PC and erythematous candidiasis (EC) in the southern data. OHL showed a positive relationship with male sex and a negative relationship with antiretroviral treatment in the northern site. Younger age and being a current smoker were positively associated with oral lesions in the southern group. **CONCLUSION:** OC, particularly PC, could be useful as a marker for immunosuppression, particularly where CD4 count cannot be determined routinely. Antifungal treatment is of benefit in the subjects who cannot afford highly active antiretroviral therapy (HAART).

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Lancet

Gender-based violence, relationship power, and risk of HIV infection in women attending antenatal clinics in South Africa

Dunkle KL, Jewkes RK, Brown HC, et al

BACKGROUND: Gender-based violence and gender inequality are increasingly cited as important determinants of women's HIV risk; yet empirical research on possible connections remains limited. No study on women has yet assessed gender-based violence as a risk factor for HIV after adjustment for women's own high-risk behaviors, although these are known to be associated with experience of violence. **METHODS:** We did a cross-sectional study of 1,366 women presenting for antenatal care at four health centers in Soweto, South Africa, who accepted routine antenatal HIV testing. Private face-to-face interviews were done in local languages and included assessment of sociodemographic characteristics, experience of gender-based violence, the South African adaptation of the Sexual Relationship Power Scale (SRPS), and risk behaviors including multiple, concurrent, and casual male partners, and transactional sex. **FINDINGS:** After adjustment for age and current relationship status and women's risk behavior, intimate partner violence (odds ratio 1.48, 95 percent CI 1.15-1.89) and high levels of male control in a woman's current relationship as measured by the SRPS (1.52, 1.13-2.04) were associated with HIV seropositivity. Child sexual assault, forced first intercourse, and adult sexual assault by non-partners were not associated with HIV serostatus. **INTERPRETATION:** Women with violent or controlling male partners are at increased risk of HIV infection. We postulate that abusive men are more likely to have HIV and impose risky sexual practices on partners. Research on connections between social constructions of masculinity, intimate partner violence, male dominance in relationships, and HIV risk behaviors in men, as well as effective interventions, are urgently needed.

Lancet 2004;363(9419):1415-1421.



Silence = complacency

Jenny's HIV diagnosis was confirmed shortly after she presented in his clinic a month ago. He prescribed an antiretroviral regimen based on his firm belief that she would derive both clinical and quality of life benefits. But within days Jenny was one of hundreds of patients on a waiting list to obtain her antiretroviral drugs through Alabama's AIDS Drug Assistance Program (ADAP)—one of more than 1,200 patients on ADAP waiting lists nationwide.

Visit www.iapac.org, to learn about how you may join the International Association of Physicians in AIDS Care (IAPAC) in advocating Jenny's right—indeed, all patients' right—to quality HIV/AIDS care and support.

PegIFN/ribavirin during acute HCV coinfection

Edwin J. Bernard

Treating hepatitis C virus (HCV) during the first six months of infection can lead to a high rate of clearance in patients coinfecting with HIV, as long as the treatment is tolerated. This according to a presentation delivered by Sanjay Bhagani and colleagues (Royal Free Hospital, London) at the 10th Anniversary Conference of the British HIV Association (BHIVA) held in Cardiff, United Kingdom.

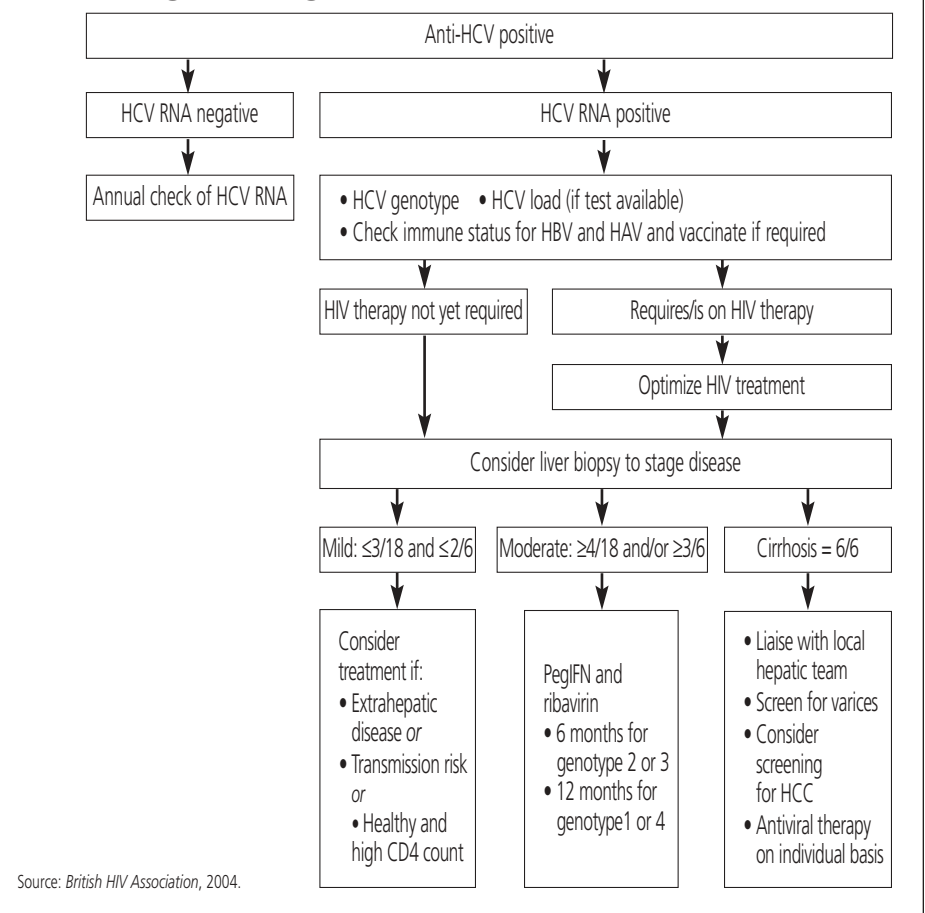
Since October 2002, 38 gay men attending the Royal Free Hospital's HIV clinic, who were already chronically infected with HIV, have been identified as newly infected with HCV. Only six of the men (15 percent) were diagnosed due to symptoms related to acute HCV infection. A further 12 men (30 percent) had their HCV infection detected during routine sexually transmitted infection (STI) screening. The majority (55 percent) were diagnosed after their routine liver function tests indicated that further investigation was warranted. All HCV infections were confirmed by positive HCV RNA (viral load) testing.

The average age of the coinfecting men was 30.5 years, median CD4 count was 514 cells/mm³ (range 207-943 cells/mm³), and 18 (48 percent) were on antiretroviral therapy at the time of diagnosis. Twenty of the men (52 percent) had also been diagnosed with another STI in the prior six months, adding weight to the assumption that the mode of transmission was sexual, since no other traditional risk factors have been found.

The majority (58 percent) were infected with genotype 1, which is more difficult to clear once the infection becomes established compared with genotypes 2 and 3; however there are few data on the success rate of treating acute genotype 1 HCV coinfection.

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Table 1. Management algorithm for HIV/HCV coinfection



All of the men were offered treatment with pegylated interferon (PegIFN) and ribavirin—the “gold standard” of chronic HCV treatment—after 12 weeks of persistently testing HCV viral load positive. Seventeen men agreed to start treatment, 13 of whom were infected with genotype 1, three with genotype 3, and one with genotype 4. Their median HCV viral load was 5.86 log₁₀ at baseline.

Since the men were diagnosed at different times, the length of follow-up reported at Cardiff ranged from 12 to 48 weeks.

• Data to week 12 were reported on 15 of the men. Eleven of the 15 on treatment (73 percent) achieved an early virological

response, which was defined as either an HCV viral load below 50 copies/ml (undetectable) or a two-log viral load decrease.

- Twenty-four week data were reported for nine men, of whom six (66 percent) achieved an undetectable HCV viral load.
- Forty-eight week data were available for seven men, of whom five (71 percent) had an undetectable HCV viral load.

Of the remaining 21 men who did not take anti-HCV therapy, nine were reported as having spontaneously cleared their HCV infection. This is a much higher number than expected—around 10 percent of all infections spontaneously clear in patients not coinfecting with HIV—although it is

possible that reappearance of HCV viral load may occur at some point in the future.

The Royal Free Hospital researchers reported a 30 percent withdrawal rate, reflecting the difficulty of tolerating interferon therapy due to its major side effect: severe depression.

These results correspond closely to the results reported at last year's BHIVA conference by Mark Nelson and colleagues from the Chelsea & Westminster Hospital. Although the on-treatment suc-

cess rate at the Royal Free Hospital appears to be around 70 percent—much higher than even the recently reported APRICOT results of 40 percent in coinfecting people with chronic HCV infection—less than half of the men offered treatment took it; of those, 30 percent were unable to tolerate its side effects for the long term.

However, considering that the majority of those who achieved treatment success were infected with genotype 1—of

whom only 29 percent achieved success in APRICOT—the researchers suggest that treatment of HCV-coinfecting patients with PegIFN and ribavirin during the acute stage of infection has a favorable response rate. At the moment, the *BHIVA Guidelines for Treatment and Management of HIV and Hepatitis C Coinfection* recommend only that physicians consider using PegIFN with or without ribavirin, with standard interferon suggested as first choice (Table 1). ■

ARCHIVED ONLINE CONFERENCE COVERAGE

XV International AIDS Conference

Bangkok, Thailand — July 11-16, 2004

The International AIDS Society and the Kaiser Family Foundation are pleased to provide daily and archived coverage from the XV International AIDS Conference.

www.kaisernetwork.org/aids2004

- Live and tape-delayed webcasts and transcripts of each day's sessions, including the opening and closing ceremonies, all plenary sessions, and selected other sessions and press conferences
- Brief text summaries of and slide presentations from select conference sessions
- Interviews with newsmakers and journalists to summarize each day's scientific, medical and political conference developments
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IN THE LIFE



Eyesusawit Shewangizaw

For more than two 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 Eyesusawit Shewangizaw, who is an internist at the Armed Forces Teaching General Hospital in Addis Ababa, Ethiopia.

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

Dale Carnegie's saying, "I cried because I had no shoes, until I met a man who had no feet."

What activities, avocations, or hobbies interest you?

I like to read easy fiction when I want to escape from this world and its responsibilities. I also like to sing biblical songs.

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

I would still like to live in Ethiopia because I feel this is where I am most needed. My second choice would be to live in the Holy Land.

Who are your mentors or real life heroes?

Mother Teresa.

With what historical figure do you most identify?

No one.

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

My favorite author is Abraham Verghese, a physician who currently lives in Texas. I recently read one of his books, and it surpasses anything that I have read up to now. I like classical music, but I am not much into paintings.

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

Biblical times.

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

I do not know, maybe I would have become a missionary or a nun.

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

The greatest achievement of humanity was creating computer technology, which has changed a lot of things in this world. The greatest failures are our inability to stop fighting each other, the big inequity between nations, and the failure to find cures for most diseases.

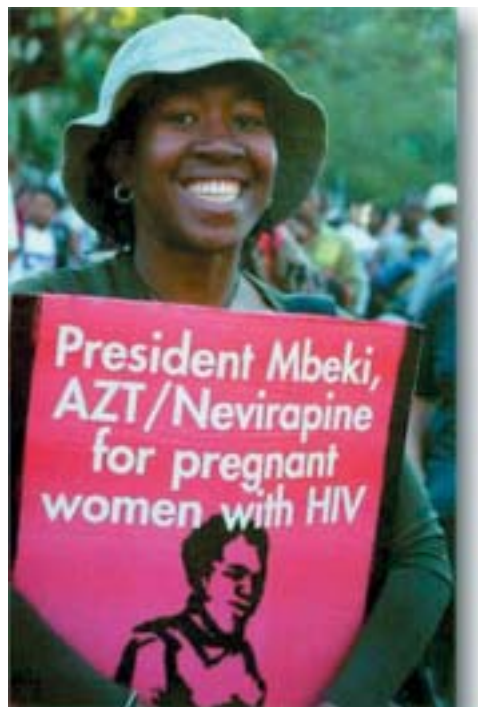
What is your prediction as to the future of our planet one full decade from present day?

A planet where people will learn from past mistakes, return to old values, and start caring for one another. ■



SAY ANYTHING


“Pictures speak louder than words” serves as the framework for this month’s “Say Anything,” which features photos from the XIII International AIDS Conference held four years ago in Durban, South Africa. As the XV International AIDS Conference (the second such conference to be held in a developing world country) opens in Bangkok this month, one basic question will trump all others: “How much progress has been made in ‘Breaking the Silence’ and, subsequently, in securing access to anti-retroviral therapy for 5.5 million men, women, and children in need worldwide?”



Photos courtesy: Bob Huff/famfAR

The Rock appears as a courtesy of World Wrestling Federation Entertainment, Inc.
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WHY DOES THE ROCK WEAR THE BRACELET?

He wears it to raise desperately needed funds for HIV/AIDS care services, education and vaccine development. Over half a million people have chosen to wear The Bracelet. What about you? Available at: The Body Shop; Kenneth Cole; Virgin Megastore; Ben Bridge Jewelers and other fine retailers. Or visit us at WWW.UNTIL.ORG or call 1-800-88-UNTIL to order. 

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.