Exploring antiretroviral interactions: Still pioneer days

Mark Mascolini

Pharmacologic science has reached the point that sustains predictions of likely antiretroviral drug-drug interactions. But as delegates at this year’s 6th International Workshop on Clinical Pharmacology of HIV Therapy in Québec learned, such predictions—much like a meteorologist’s weather forecast—can be wrong.
Time-delimited goals are widely used by not-for-profit and charitable organizations. As chief executive of the International Association of Physicians in AIDS Care (IAPAC), I oversee myriad initiatives association-wide, the majority of which are time-delimited in nature.

The value of this management strategy is without a doubt its imperative for quick and effective action. Its application has been particularly valuable around public health goals such as the Pan American Health Organization (PAHO)’s goal of eradicating polio in the Americas by 1990, and the Global Alliance to Eliminate Leprosy’s goal of eliminating leprosy throughout the world by 2005. While goals may not be met by an exact deadline, the flurry of activity they spark and the momentum they carry forward are invaluable.

Two specific time-delimited goals set by the World Health Organization (WHO) during the past 40 years stand out in my mind as examples of why such a management mechanism should be employed to advance public health goals.

The WHO launched its Smallpox Eradication Programme in 1967—a campaign whose success would vanquish smallpox, essentially making this the first virulent disease to have been eradicated in the history of modern medicine. At the year of its launch, some 10 to 15 million cases were estimated to occur annually in more than 30 endemic countries, and it threatened to kill a third of those infected. No cases of smallpox have occurred in the world since 1977, in large measure because of the worldwide smallpox vaccination program spearheaded by the WHO and implemented by public health authorities in endemic countries. A global commission certified in 1979 that smallpox had been eradicated. The 33rd World Health Assembly officially accepted this certification in 1980.

The WHO, in partnership with institutions such as the International Trachoma Initiative and Sight Savers International, launched a campaign in 1996 to eliminate trachoma worldwide by the year 2020. This blinding infectious disease is responsible for at least 3% of the world’s preventable blindness and, according to the WHO, 84 million cases of active disease are in need of treatment. While many of the interim goals of the Global Elimination of Trachoma (GET) campaign have not yet been reached, trachoma has been eliminated in several previously hyperendemic countries, such as Morocco, where in three years from the campaign’s launch, the prevalence of trachoma in children was reduced by 90%. The WHO and its partners hope to achieve similar victories in the 48 other endemic countries through a combination of community-targeted interventions known by the acronym “SAFE,” which stands for surgery for trichiasis, antibiotics, facial cleanliness, and environmental improvement.

Thus, when the WHO announced in 2002 its time-delimited goal of expanding access to antiretroviral therapy (ART) to 3 million people in the developing world by 2005, and recognizing the value that such target-setting would have on our collective cause, IAPAC immediately applauded WHO and signed on as a “3 by 5” partner. Several of my IAPAC colleagues and I participated in numerous WHO consultations held in Geneva around various aspects of ART scale-up, but primarily around human capacity-building to deliver ART across a continuum of care. And, indeed, I communed with my non-profit sector colleagues—including representatives from the Association of Nurses in AIDS Care (ANAC), Foundation for Professional Development (FPD), International AIDS Society (IAS), PharmAccess, and others—much more regularly under the auspices of WHO consultations.

Then, halfway through the process, “3 by 5” partners became less “partners” and more “cheerleaders” in the effort not only to help publicize the good work that was being done, but to ignore or at least remain silent about any potential shortfalls of, or any misgivings about, the chosen method for achieving our collective goal. I expect to be roundly criticized in some circles for articulating IAPAC’s frustration. Indeed, by default, I have already been characterized by individuals...

Continued on page 217
1. The US Centers for Disease Control and Prevention (CDC) in January 2000 reported that for the first time, new HIV infections were identified in more black and Hispanic gay men than in white gay men in the United States. African Americans made up 57% of all new HIV infections, though only 13% of the US population is African-American.

2. It was reported in early 2000 that for the first time in the United Kingdom, the number of newly diagnosed HIV infections acquired through heterosexual contact surpassed the number of infections acquired through homosexual contact.

3. Preliminary studies of what would later be termed structured treatment interruptions (STIs) were presented at the 7th Conference on Retroviruses and Opportunistic Infections (CROI). The studies implied that in some cases a temporary break from antiretroviral therapy (ART) did not result in increased viral load or antiretroviral drug resistance.

4. In Botswana, it was estimated that as many as one in four adults and four in 10 pregnant women were infected with HIV, and it was predicted that two thirds of 15-year-olds in that country would die of AIDS before reaching age 50. Botswana's president, Festus Mogae, announced that new contributions, including US$50 million donated by the Bill and Melinda Gates Foundation, would allow his country to provide ART to all HIV-infected pregnant women and children.

5. The Clinton Administration formally declared HIV/AIDS a threat to US national security, arguing that the global spread of AIDS could topple foreign governments, spark ethnic wars, and erode decades of work building free-market democracies abroad. However, later in the year, the US Institute of Medicine released a report criticizing the Clinton Administration for failing to develop a comprehensive and effective plan to combat the disease in the United States.

6. Five pharmaceutical companies offered in May 2000 to negotiate steep price reductions for antiretroviral drugs for developing countries. In July 2000, the United States announced a plan to offer US$1 billion in loans to sub-Saharan African nations, to help those countries purchase antiretroviral drugs and medical services. Leaders of many African nations believed that accumulating more debt was not a solution to the HIV/AIDS crisis and rejected the offer, suggesting that lower drug prices and agreements to allow compulsory licensing would be more effective.

7. The US Food and Drug Administration (FDA) issued accelerated approval for Kaletra, a fixed-dose combination antiretroviral drug containing the protease inhibitors lopinavir and ritonavir.

8. The US FDA issued approval of Trizivir, a fixed-dose combination antiretroviral drug containing abacavir, lamivudine, and zidovudine.

9. The XIII International AIDS Conference, held in Durban, South Africa, was the largest international AIDS conference ever held, and the first that took place in a developing country.

10. The World Health Organization (WHO) estimated that between 5% and 10% of HIV infections worldwide were the result of blood transfusions, where the donors were either not screened or inadequately screened for HIV.

References

4. Harvard University Gazette. Harvard AIDS Institute opens HIV laboratory in Botswana. February 17, 2000; Gottlieb S. UN says up to half the teenagers in Africa will die of AIDS. BMJ. 2000;321:67;  
FDA approves tipranavir

The US Food and Drug Administration (FDA) granted accelerated approval on June 22, 2005, of tipranavir (TPV), a new protease inhibitor (PI) meant to be co-administered with 200 mg of ritonavir (RTV) as part of combination antiretroviral therapy for highly treatment-experienced patients or those who have HIV-1 strains resistant to multiple protease inhibitors.

The approval of tipranavir/ritonavir (TPV/r) is based on analyses of plasma HIV-1 RNA levels in two controlled phase III studies of TPV/r of 24 weeks duration. Both studies were conducted in clinically advanced, treatment-experienced adults with evidence of HIV-1 replication despite ongoing antiretroviral therapy. In both studies, a significantly greater percentage of HIV-positive patients taking TPV/r achieved treatment response than the comparator group (40% versus 18%). Treatment response was defined as a confirmed 1 log₁₀ or greater decrease in HIV RNA from baseline.

The approved dose of TPV is 500 mg taken with 200 mg of RTV, twice daily with food. Tipranavir must be co-administered with 200 mg of RTV to exert its therapeutic effect. Failure to correctly co-administer TPV with the RTV boost will result in reduced plasma levels of TPV that will be insufficient to achieve the desired antiviral effect. Taking the drug with food improves absorption.

According to the FDA, the following points should be considered when initiating therapy with TPV/r:

- The use of other active agents with TPV/r is associated with a greater likelihood of treatment response.
- Genotypic or phenotypic resistance testing and/or treatment history should guide the use of TPV/r. The number of baseline primary PI mutations affects the virologic response to TPV/r.
- Because TPV can cause serious liver toxicity, liver function tests should be performed at initiation of therapy with TPV/r and monitored frequently throughout the duration of treatment.
- Use caution when prescribing TPV/r to patients with elevated transaminases, hepatitis B or C coinfection, or other underlying hepatic impairment.
- Tipranavir administered with low-dose RTV may cause many drug interactions. Therefore, patients should report to their health care provider the use of any other prescription or non-prescription medication or herbal products, particularly St. John’s wort. Certain medicines, such as antiarhythmics, antihistamines, ergot derivatives, any medication that speeds up the digestive tract, herbal products, some cholesterol-lowering drugs, and some psycho-active drugs should never be given with TPV plus RTV because of potentially serious side effects.

Patients receiving estrogen-based birth control pills or patches should be instructed that additional or alternative forms of birth control should be used when taking TPV.

In making its announcement, the FDA also noted the following issues:

- The extensive drug-drug interaction potential of TPV/r when co-administered with multiple classes of drugs must be considered prior to and during TPV/r use.
- The risks and benefits of TPV/r have not been established in treatment-naïve adult patients or pediatric patients.
- There are no study results demonstrating the effect of TPV/r on clinical progression of HIV-1.

Safety information

The most commonly reported (≥3%) adverse reactions were diarrhea, nausea, fatigue, headache, and vomiting. The most commonly reported laboratory abnormalities were elevated liver enzymes, cholesterol, and triglycerides.

Hepatotoxicity

The TPV label includes a “black box” warning regarding hepatotoxicity. Specifically, TPV co-administered with low-dose RTV has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. Extra vigilance is warranted in patients with chronic hepatitis B or C coinfection, as these patients have an increased risk of hepatotoxicity.

All patients should be followed closely with clinical and laboratory monitoring, especially those with chronic hepatitis B or C coinfection, as these patients have an increased risk of hepatotoxicity. Liver function tests should be performed prior to initiating therapy with TPV/r, and frequently throughout the duration of treatment.

In addition, TPV is contraindicated in patients with moderate and severe (Child-Pugh Class B and C, respectively) hepatic insufficiency.

Sulfonamide allergy

Tipranavir should be used with caution in patients with a known sulfonamide allergy. Tipranavir contains a sulfonamide component. The potential for cross-sensitivity between TPV and drugs in the sulfonamide class is unknown.

Rash

Mild to moderate rashes, including urticarial rash, maculopapular rash, and possible photosensitivity have been reported in subjects receiving TPV/r. In phase II and III trials, rash was observed in 14% of females and in 8% to 10% of males receiving TPV/r. Additionally, in one drug interaction trial in healthy female volunteers given a single dose of ethinyl estradiol (a hormonal contraceptive) followed by TPV/r, 33% of subjects developed a rash. Rash accompanied by joint pain or stiffness, throat tightness, or generalized pruritus has been reported in both men and women receiving TPV/r.
Theo Smart

The best way of honoring the memory of Nkosi Johnson and many other children who met premature deaths at the hands of HIV/AIDS is to end denialism now!” Mamphela Ramphele delivered that message to a cheering audience at the opening of the 2nd South African AIDS Conference, held June 7-10, 2005, in Durban. Ramphele, who is a prominent South African physician and a highly distinguished African scholar, urged fellow South Africans to transcend their past and work together to ensure the human rights of people with AIDS.

Ramphele has received numerous prestigious national and international awards acknowledging her leadership role in advancing development issues and spearheading projects for disadvantaged persons throughout South Africa. She was the first black woman to serve as Vice Chancellor of the University of Cape Town, and was a former Managing Director of the World Bank.

It was thus no surprise that she was chosen to deliver the inaugural memorial lecture in honor of Nkosi Johnson, the HIV-positive South African boy who confronted the world (and his president) about HIV five years ago, on the stage of the 12th International AIDS Conference in Durban. “I want people to understand about AIDS,” he said then, urging the world to “care for us and accept us…we are human beings.” Johnson died a year later. Now, four years later, the treatment for which he pleaded is only just starting to reach South African children.

“But why would an 11-year-old child have to make such an impassioned plea in the South Africa of 2000?” Ramphele asked. “Is this not a country with a government that has explicitly stated that its governance principles are based on Batho Pele (People First)? What has gone wrong?”

Ramphele said that HIV/AIDS is like a mirror in the face of South African society, forcing the country to see itself as it really is, and not how it would like to be seen. “Like any face, ours bears the scars of the past,” but she added it also shows “the impact of the realities of today.”

HIV/AIDS in South Africa since apartheid

The new South Africa has a constitution that is “second to none” in committing to protect “the fundamental rights of everyone.” However, Ramphele stated, “the gap between those ideals and our practices in society is large.”

She attributed part of the gap to the difficulty of overcoming the legacy of apartheid, but she also acknowledged that much of the problem comes from weak government capacity to implement policy commitments and to monitor itself. “The failure to acknowledge and correct deficits since 1994 has left us in a weak position to live out our commitments,” she said.

Ramphele also argued that stigma still pervades South African society and constrains the response to the epidemic. “The quality of our society will be judged by how well we treat the most vulnerable among us. We are not at the moment doing well on that score.”

Part of the problem dealing with HIV/AIDS is its link to sexuality. “All the cultures we bring into the new South Africa are prudish about talking about sex. We just do it.” Also, customs such as polygamy, multiple
The majority of South Africans scientific mistrust of the racist system that denied based policy-making was constrained by making domain of government. Evidence-

male, urban-based, and outside the policy-

But the scientists were largely white,

runner in comprehensive care and treat-

economic resources to have been a front-

depth of scientific know-how and

them,” she said.

using the resources we have to address

from acknowledging our problems and

South Africa. “We have a serious problem

why denialism has been so persistent in

To add insult to injury, the same racist system had over the centuries in many parts of the world stigmatized black male sexuality as dangerous and driven by uncontrollable lust. Unless we acknowledge the pain of those so stigmatized, we are unlikely to overcome our mistrust and build a better life for all.”

But she called for those wounded “to transcend the past and take ownership of shaping a future of dignity for all.”

Transcending the past

Ramphele also called for scientists to stand up to the denialists and profiteers bent on misleading the public. “The medical profession needs to play the role of watchdog for poor, vulnerable people... How can we allow the current confusion between the role of specific treatment with antiretrovirals and the benefits of good nutrition and supplementary nutritional agents such as vitamins? It sounds so medieval.”

She reminded the audience of the sanatoria to which tuberculosis (TB) patients went before anti-mycobacterial drugs were available. “People received the best care and nutrition possible... and they died. Remember that those early TB drugs too had toxic side effects but they were better than placebos.”

She said that confusing advice to those already overwhelmed by the trauma of HIV/AIDS should not be permitted. Finally, she called for an end to denialism.

“Our country is over ten years old now, we need to take ownership of shaping our country’s future and create a better life for all. Blaming apartheid has its limits, just like blaming one’s parents for one’s failures has it limits too. We need to transcend our past and build a better future by playing to our strengths and minimizing our weaknesses.”

Theo Smart

efforts to improve the care and treatment of South Africans with HIV/AIDS are often hampered by misunderstandings and poor relations between Western health care workers and the community-based African traditional healers (or sangomas) to whom many people first turn when they have a medical complaint. However, a new project launched in the Nelson R. Mandela School of Medicine/University of KwaZulu-Natal (UKZN) in Durban is trying to build bridges and improve collaboration with traditional healers caring for people with HIV/AIDS.

It has been estimated that 80% of South Africans see sangomas on a regular basis and that there are around 200,000 sangomas in the country; but efforts to test and treat people with antiretroviral therapy (ART) often leave the community sangoma out of the loop, leading patients to disregard their physician’s advice, or take herbal remedies that may have dangerous interactions with pharmaceutical drugs they are taking. However, working closely with traditional healers could reduce workload, improve patient care, and give treatment programs key strategic allies and counselors who live within the patient’s own community.

Speaking at a satellite meeting preceding the 2nd South African AIDS Conference, James Hartzell, an adjunct lecturer at the Nelson R. Mandela School of Medicine/UKZN, said, “The medical school has long had a strategy to develop a focus on complementary systems of medicine, including African health care systems (AHCS), Indian systems of medicine (eg, ayurvedic), Chinese systems of medicine (eg, traditional Chinese medicine), and other traditional, complementary and alternative systems.”

The UKZN Department of Family Medicine hosts lectures on complementary systems of medicine for undergraduate and graduate medical students, and has a number of research initiatives under development.

One of the first to be approved by the faculty is the AHCS Research Network. A memorandum of understanding was signed in October 2003 between the school and the KwaZulu-Natal Traditional Healers’ Council (including the Ethekwini [Durban] Traditional Healers’ Council), Mwelela Kweliphesheya (a development arm of KwaZulu-Natal Indigenous Healers), and the Umgogodla Wesizwe Trust. An HIV/AIDS task team was established from KwaZulu-Natal’s 11 health districts; and the US Department of State funded two workshops to discuss future directions for collaboration.

These discussions generated the first major AHCS proposal: The Saving Lives: Biomedical and Traditional Healing Collaboration on HIV/AIDS, which received funding last year from the US President’s Emergency Plan For AIDS Research (PEPFAR). The collaborative project is in the process of training 350 traditional healers (in five one-week long trainings) on HIV/AIDS awareness, voluntary counseling and testing, home-based care, and ART awareness.
Specific components of the project include:

- **Guidelines development.** The project is working to develop joint HIV/AIDS clinical guidelines using family medicine guidelines (which Hartzell says have many similarities with the traditional healer approach), the Ethekwini health guidelines, KwaZulu-Natal’s Department of Health guidelines, and traditional healer guidelines that AHCS has been helping to formalize (based upon informal, unwritten guidelines that already exist).

- **Two-way referral system development.** To some extent, an informal system of referral already exists between sangomas and health care facilities. But, said Hartzell, “Traditional healers complain that it is largely in one direction (from the sangomas to the clinics).” Frequently, patients move back and forth from the sangoma to the clinic, especially when they want to hear an alternative diagnosis after testing positive for HIV, but the traditional healers do not know what is happening at the clinic. “Traditional healers already send referral letters to clinics and are just asking for at least basic information back from the biomedical team (which is often hostile to them), such as what were patients given in terms of treatment,” Hartzell explained.

  Forming better two-way communication could be vital to a patient’s health. Hartzell suggests that “traditional healers can make a big impact on patient compliance and OI management with good collaboration from the biomedical team.”

  However, confidentiality issues must be clarified before physicians will feel free to share patient information with traditional healers, and the project is working with the Department of Health on these issues.

- **Medical kit supply.** Most traditional healers work in resource-constrained settings, seeing an average of five HIV-positive patients a day, and yet most of them do not even have rubber gloves. The project is working to supply them with a modified version of the KwaZulu-Natal Department of Health (KZN DOH) Home-Based Care Kit.

- **Introduction of record-keeping systems.** “This underlines the success of the entire project,” said Hartzell, “but is a brand-new concept to most traditional healers.” Even so, it has already been agreed to and advocated by the traditional healer councils.

However, this is one of the project’s greatest challenges, because of the issue of illiteracy, which means systems have to use pictograms and check boxes. Hartzell said they may experiment with tape recordings as well.

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**An ounce of prevention**

Counsel your HIV-positive patients about safer sex. An ounce of prevention is worth everyone’s effort!
Exploring antiretroviral interactions: Still pioneer days
ost North American schoolchildren know that Samuel de Champlain founded Québec, the oldest city on the continent. But it wasn’t easy.

Champlain had already outlasted three gelid winters in Acadia, though most of his troop succumbed to the cold. By 1608 he’d had enough and moved south—to Québec. The doughty explorer counted only eight surviving followers when the ice-clad St. Lawrence River yielded to spring.

Persistence paid off. As Montreal virologist Mark Wainberg (McGill University) noted in opening the 6th International Workshop on Clinical Pharmacology of HIV Therapy, Québec became the base of exploration that ended only at the continent’s other side.

Antiretroviral pharmacology has survived more than four mean winters, but a workshop like the one in Québec can convince optimists that these are still early days. Research has barely started scratching through a continent-thick list of potential antiretroviral interactions. And new antiretrovirals—along with other drugs people with HIV take—are coming all the time.

Pharmacologic science has reached the point that sustains predictions of likely interactions. But this workshop showed that predictions can be wrong.

On top of that, people change. Kids grow up. Adults grow old. They get fat. They get hepatitis. All of these permutations and many more—workshop attendees learned—permeate the metabolic machinery in ways overt and subtle.

This workshop review begins with one variable that changes ceaselessly, and one that hardly ever shifts—age and gender. Other topics considered are:

- Interactions with protease inhibitors (PIs)
- PI toxicities
- Interactions with tenofovir (TDF)
- Prospects for fusion and entry inhibitors
- Therapeutic drug monitoring

Editor’s note: This article first appeared at www.HIVPharmacology.com and is reprinted here with permission from Virology Education, Utrecht, The Netherlands.

### Table 1. LPV troughs in older versus younger people

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<th>Week 24</th>
<th>Week 36</th>
<th>Week 92</th>
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<tr>
<td>45 years old or older</td>
<td>8.0</td>
<td>5.8</td>
<td>6.7</td>
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<tr>
<td>18 to 30 years old</td>
<td>2.7</td>
<td>3.5</td>
<td>5.0</td>
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<tr>
<td>P</td>
<td>0.001</td>
<td>0.38</td>
<td>0.16</td>
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Older people had higher lopinavir (LPV) levels in one study, but not in another. In the second study, though, seniors saw higher efavirenz (EFV) concentrations.

Earlier work charted dwindling activity of CYP3A4, the key PI-metabolizing enzyme, in older people.1 Less CYP3A4 means slower PI metabolism, and that should mean higher drug levels. But previous studies in people taking antiretrovirals saw no apparent effect of age on PI metabolism—perhaps because those studies were too small.

For the still unsated, a long table lists the many studies that saw no hurtful interactions with antiretrovirals.

### AGE, GENDER, WEIGHT, AND ANTIRETROVIRALS

Older people had higher lopinavir (LPV) levels in one study, but not in another. In the second study, though, seniors saw higher efavirenz (EFV) concentrations.

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Teresa Parsons (Johns Hopkins University, Baltimore) and AIDS Clinical Trials Group (ACTG) collaborators managed a bigger analysis in a pharmacologic substudy of treatment-naïve people starting standard-dose LPV/ritonavir (RTV) with emtricitabine (FTC) and stavudine (d4T) [abstract 40, poster 3.6]. They prospectively measured LPV troughs 10 to 14 hours after dosing in 44 people, half of them 18 to 30 years old (median 26 years) and half 45 years old or older (median 50 years).

Gauging LPV troughs at weeks 24, 36, and 96, Parsons logged significantly higher levels in the older contingent. Though the overall difference fell just short of statistical significance (P = 0.056), the difference at week 24 was significant (P = 0.001) (Table 1).

In a multivariate analysis adjusted for age, hours since last dose, week of blood draw, and gender, only age independently predicted a higher LPV trough (P = 0.047). In a multivariate model reckoning age and gender, age alone predicted higher LPV troughs at week 24 (P = 0.0002), but age lost predictive significance at week 36 (P = 0.18) and week 92 (P = 0.33).

Parsons stressed that LPV levels overlapped considerably between younger folk and their elders, but most of the very high levels turned up in the older group—including the highest reading in a 79-year-old.

In a retrospective British study EFV troughs proved significantly higher in postmenopausal women than in premenopausal women [abstract 54, poster 4.8]. This study failed to find a significant LPV trough difference in pre- and postmenopausal women, perhaps because the cohort included only seven postmenopausal women taking the PI. Earlier work chalked up 20% lower CYP3A4 content in postmenopausal women,2 but had not eyed the potential effect of age and menopausal status on CYP2D6, the main EFV metabolizer.

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Sara Gibbons (University of Liverpool) ransacked records from Liverpool’s therapeutic drug monitoring (TDM) service to cull LPV levels measured 10 to 14 hours after dosing and EFV concentrations tallied eight to 16 hours after treatment in three groups of women:

- Premenopausal: under 40 years old
- Perimenopausal: 40 to 50 years old
- Postmenopausal: over 50 years old

The analysis excluded levels below 100 ng/mL—a likely signal of bad adherence. The only significant difference arose in the comparison of premenopausal and postmenopausal women taking EFV (Table 2).

Gibbons noted two study limitations—using age as an indicator of menopausal status and lack of data on contraceptive steroid or hormone replacement therapy.

But together these studies suggest that older people may run a higher risk of PI or nonnucleoside reverse transcriptase inhibitor (NNRTI) toxicity.

### How gender and weight affect efavirenz and saquinavir

Lower weight—but not gender—predicted higher EFV sums in a retrospective analysis of people taking 800 or 600 mg of the NNRTI with rifampin (rifampicin) [abstract 19, poster 2.12]. Lisa Almond and University of Liverpool colleagues sifted the group’s 1999 to 2004 TDM service data, looking for adults taking EFV and rifampin and scoring a drug level above 100 ng/mL to verify adherence.

Efavirenz concentrations tallied eight to 16 hours after dosing did not differ significantly in 111 people taking 800 mg of the NNRTI and 20 taking 600 mg—both with rifampin. Neither group had a significantly higher number of people outside the 1,000- to 4,000-ng/mL target range. Nor did EFV levels differ between 58 men and 54 women taking 800 mg of EFV with rifampin or in 281 men and 79 women taking EFV without the tuberculosis (TB) drug.

Body weight did make a difference. Among the 111 people taking 800 mg of the NNRTI with rifampin, 42.5% of those weighing under 60 kg had an EFV reading above 4,000 ng/mL compared with 25.3% of those weighing more (odds ratio [OR] 0.46, 95% confidence interval [CI] 0.19 to 1.14, \( P = 0.09 \)).

Higher weight meant a lower EFV trough in both men (\( \text{rho} = -0.27, P = 0.003 \)) and women (\( \text{rho} = -0.15, P = 0.004 \)). Nested regression analysis linked weight (\( P = 0.03 \)) but not gender or EFV dose to EFV tabs topping 4,000 ng/mL.

While gender did not affect EFV quotients, one might expect a gender difference in PI levels because research confirms higher hepatic CYP3A4 expression in women. That would speed metabolism of CYP3A4 substrates like saquinavir (SQV), and stepped-up metabolism usually means faster clearance and lower levels. But most PIs these days come with a kick from RTV, a fierce CYP3A4 inhibitor.

Ritonavir seems to be winning the metabolism contest in women taking it to boost SQV—stunting elimination of the PI and expanding its exposure. Laura Dickinson (University of Liverpool) confirmed earlier studies showing higher SQV levels in women than in men in a retrospective analysis of 28 men and six women taking 1,000/100 mg of SQV/RTV twice daily [abstract 9]. Dickinson extended previous work by weighing drug transporter expression as a possible mechanism behind this gender difference in a separate study of 63 men and 30 women.

This retrospective analysis charted much higher SQV and RTV levels in the six women than in the 26 men. Gender did not affect the terminal half-life of either PI (Table 3).

Looking at drug transporter expression on peripheral blood mononuclear cells (PBMCs), Dickinson found that women had significantly lower levels of P-glycoprotein (MRP) 1 (0.15 versus 0.35, \( P = 0.018 \)). Whether transporter expression on PBMCs closely reflects expression in the intestine and other sites is unknown.

### Table 2. EFV and LPV levels in older versus younger women

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<td></td>
<td>n</td>
<td>Median</td>
<td>Interquartile range</td>
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<tr>
<td>Premenopausal</td>
<td>85</td>
<td>1,990</td>
<td>1,500 to 3,361</td>
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<tr>
<td>Perimenopausal</td>
<td>38</td>
<td>1,847</td>
<td>1,418 to 3,025</td>
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<tr>
<td>Postmenopausal</td>
<td>18</td>
<td>2,516*</td>
<td>2,135 to 4,092</td>
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<tr>
<th></th>
<th>LPV</th>
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<tbody>
<tr>
<td>Premenopausal</td>
<td>68</td>
<td>6,786</td>
<td>3,620 to 9,112</td>
</tr>
<tr>
<td>Perimenopausal</td>
<td>41</td>
<td>7,142</td>
<td>4,843 to 8,928</td>
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<tr>
<td>Postmenopausal</td>
<td>7</td>
<td>5,621*</td>
<td>3,518 to 6,647</td>
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*\( P = 0.046 \) versus premenopausal.


### Table 3. Median SQV and RTV levels in women versus men

<table>
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<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>( P )</th>
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<tr>
<td>SQV AUC(_{0-12\text{h}}) (ng•h/mL)</td>
<td>13,804 (2,865 to 45,622)</td>
<td>24,774 (18,836 to 48,367)</td>
<td>0.053</td>
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<tr>
<td>SQV trough (ng/mL)</td>
<td>271 (70 to 2,071)</td>
<td>786 (659 to 1,465)</td>
<td>0.053</td>
</tr>
<tr>
<td>SQV peak (ng/mL)</td>
<td>2,343 (542 to 7,131)</td>
<td>4,373 (2,419 to 7,843)</td>
<td>0.053</td>
</tr>
<tr>
<td>SQV half-life (h)</td>
<td>2.97 (1.84 to 4.51)</td>
<td>3.23 (2.87 to 3.70)</td>
<td>0.55</td>
</tr>
<tr>
<td>RTV AUC(_{0-12\text{h}}) (ng•h/mL)</td>
<td>7,587 (1,556 to 16,929)</td>
<td>15,421 (11,155 to 21,195)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RTV trough (ng/mL)</td>
<td>192 (73 to 634)</td>
<td>558 (385 to 839)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RTV peak (ng/mL)</td>
<td>1,052 (237 to 2,195)</td>
<td>2,818 (1216 to 4,395)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RTV half-life (h)</td>
<td>3.35 (2.01 to 9.62)</td>
<td>3.01 (2.64 to 3.50)</td>
<td>0.36*</td>
</tr>
</tbody>
</table>

*\( n = 5. \)

\( \text{AUC}_{0-12\text{h}} = \text{area under the concentration-time curve over 12 hours.} \)
More reliable nevirapine dose for children?

With the steep plunge in HIV prevalence among children in developed countries, kids stand likely to remain a pharmacologically understudied contingent until more trials in unhappier lands bear fruit. That gap poses a stern challenge since antiretroviral dosing is vastly more complicated in ever-changeful children than in adults.

Big Western trial groups such as the Paediatric European Network for Treatment of AIDS (PENTA) and ACTG have tried to fill that gap, as have researchers in countries with still woefully flush pediatric cohorts like South Africa and Thailand. Edmund Capparelli (University of California, San Diego) came to the workshop with data from five ACTG trials that cataloged 2,449 nevirapine (NVP) concentrations in infants and children ranging in age from 40 under six months old, 46 between six months and two years, 152 between two and six, 206 between six and 12, and 51 older than 12.

The ACTG cohort represented a close split between boys (54%) and girls (46%). Reflecting HIV epidemiology in the United States, the group consisted mainly of blacks (54%) and Hispanics (31%). The analysis rested on large numbers of participants taking lamotrigine [abstract 37]. The results suggested the need to double NVP AUCs across age groups:

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>NVP</th>
<th>NVP + NFV</th>
<th>NVP + RTV</th>
<th>NVP + NFV + RTV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>53.6 (-10%)</td>
<td>69.5 (+9%)</td>
<td>67.1 (+6%)</td>
<td>87.0 (+37%)</td>
</tr>
<tr>
<td>5</td>
<td>63.9 (+11%)</td>
<td>70.6 (+11%)</td>
<td>80.0 (+26%)</td>
<td>88.3 (+39%)</td>
</tr>
<tr>
<td>14</td>
<td>56.6 (-11%)</td>
<td>54.3 (-15%)</td>
<td>70.7 (+11%)</td>
<td>67.9 (+7%)</td>
</tr>
</tbody>
</table>

AUC = area under the concentration-time curve over 12 hours; CI = confidence interval.

More trials in unluckier lands bear fruit. The ACTG ran two population pharmacokinetic analyses to hone a model that correlated dose with a target area under the concentration-time curve (AUC) of 63.6 µg•h/mL (Table 4). The FDA dose was 400/100 mg of LPV/RTV on lamotrigine until Manon van der Lee (Radboud University Nijmegen Medical Center, The Netherlands) tested high-dose RTV induces glucuronidation of certain drugs, and lamotrigine’s metabolism depends on hepatic glucuronidation. But no one assessed the effects of low-dose RTV on lamotrigine until Manon van der Lee (Radboud University Nijmegen Medical Center, The Netherlands) tested standard-dose LPV/RTV in 24 healthy volunteers taking lamotrigine [abstract 12]. Results suggested the need to double lamotrigine’s dose with these PIs.

Twelve women and 12 men started lamotrigine at 50 mg daily for two days, then upped the dose to 100 mg twice daily on study days three through 10. At that point they added 400/100 mg of LPV/RTV twice daily for the next 10 days.

Comparing day 10 and 20 lamotrigine troughs, the Nijmegen team planned to stop the study or adjust the dose depending on results:

- <20% decrease: stop study
- 20% to 33% decrease: adjust to 150 mg twice daily
- 34% to 66% decrease: adjust to 200 mg twice daily

Discovering the interactions between PIs and other drugs (including other PIs) is an odyssey more trying and less terminable than the fraught adventures of Homer’s hero.

Development of every new PI, every new formulation, and every new dose demands another set of studies to steer the drug between the Scylla of side effects and the Charybdis of incompetence. And every time someone takes a PI with another drug, the fretful pharmacologist must ensure that other drug is no Circe set to transmute PIs into swinish distraction.

Workshop attendees heard news on potentially pernicious interactions between PIs and lamotrigine, tacrolimus, prednisone, rifampin, and paroxetine. Other studies explored PI-PI liaisons and how liver disease affects boosted PI levels.

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**PROTEASE INHIBITOR INTERACTIONS**

Lopinavir lowers lamotrigine levels

Epileptics with HIV take lamotrigine, as do some people with peripheral neuropathy. High-dose RTV induces glucuronidation of certain drugs, and lamotrigine’s metabolism depends on hepatic glucuronidation. But no one assessed the effects of low-dose RTV on lamotrigine until Manon van der Lee (Radboud University Nijmegen Medical Center, The Netherlands) tested standard-dose LPV/RTV in 24 healthy volunteers taking lamotrigine [abstract 12]. Results suggested the need to double lamotrigine’s dose with these PIs.

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Workshop attendees heard news on potentially pernicious interactions between PIs and lamotrigine, tacrolimus, prednisone, rifampin, and paroxetine. Other studies explored PI-PI liaisons and how liver disease affects boosted PI levels.
In the 18 volunteers who completed 20 days of treatment, van der Lee found lamotrigine troughs halved compared with day 10 levels (Table 5). With the doubled dose of 200 mg twice daily, 15 people completed the study at day 31. The inflated dose brought total lamotrigine exposure and peak levels back to day 10 levels, while the trough improved markedly.

Lopinavir and RTV AUCs and troughs on day 20 matched those of historical controls. The study also assessed levels of lamotrigine’s main metabolite, but those results had not been analyzed at the time of the workshop.

The Nijmegen group concluded that clinicians should bump lamotrigine to 200 mg twice daily in people taking the antiepileptic agent lamotrigine and antiretrovirals remain largely undefined. Anne-Marie Taburet (Bicêtre Hospital, Paris) learned that EFV and nucleoside reverse transcriptase inhibitors (NRTIs) have little effect on lamotrigine metabolism, but LPV/RTV and NFV slow elimination of the drug to a glacial pace [abstract 26, poster 2.24]. This small study showed, however, that well-planned monitoring permits accurate dose adjustment.

Taburet tracked tacrolimus and antiretroviral levels in eight people coinfected with hepatitis C virus (HCV) who had orthotopic liver transplantation with a CD4 count above 150 cells/mm³ and an HIV infection with hepatitis C virus (HCV) who had retroviral levels in eight people coinfected with hepatitis C virus (HCV) who had

### Table 6. Effect of low-dose RTV on prednisolone exposure

<table>
<thead>
<tr>
<th></th>
<th>GMR (90% CI) day 4 vs baseline</th>
<th>GMR (90% CI) day 14 vs baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng·h·mL⁻¹)</td>
<td>1.37 (1.27 to 1.47)*</td>
<td>1.28 (1.19 to 1.37)*</td>
</tr>
<tr>
<td>Clearance (L/h)</td>
<td>0.73 (0.68 to 0.78)*</td>
<td>0.78 (0.64 to 0.92)*</td>
</tr>
<tr>
<td>Terminal half-life (h)</td>
<td>1.33 (1.20 to 1.46)*</td>
<td>1.15 (0.98 to 1.34)</td>
</tr>
<tr>
<td>Peak (ng/mL)</td>
<td>1.11 (0.93 to 1.29)</td>
<td>1.09 (0.91 to 1.27)</td>
</tr>
</tbody>
</table>

*P < 0.002.

Protease inhibitor impact on tacrolimus and prednisone

With liver transplantation a life-saving option for many people with well-controlled HIV infection, the interactions between the antirejection agent tacrolimus and antiretrovirals remain largely undefined. Anne-Marie Taburet (Bicêtre Hospital, Paris) learned that EFV and nucleoside reverse transcriptase inhibitors (NRTIs) have little effect on lamotrigine metabolism, but LPV/RTV and NFV slow elimination of the drug to a glacial pace [abstract 26, poster 2.24]. This small study showed, however, that well-planned monitoring permits accurate dose adjustment.

Taburet tracked tacrolimus and antiretroviral levels in eight people coinfected with hepatitis C virus (HCV) who had orthotopic liver transplantation with a CD4 count above 150 cells/mm³ and an HIV load below 50 copies/mL. Three were taking LPV/RTV, two NFV, two EFV, and one a triple-NRTI regimen. They stopped their antiretrovirals on the transplant day and restarted 10 days later. The immunosuppressive regimen included tacrolimus and prednisone.

Measuring tacrolimus levels when liver function stabilized (about 10 days after transplantation), Taburet recorded oral clearances ranging from 5.3 L/h to 19.4 L/h. After 10 days of NFV, clearance of the transplant drug plunged to a range of 1.1 to 3.0 L/h, and after 10 days of LPV/RTV to 0.5 to 0.9 L/h. With LPV/RTV the half-life of tacrolimus stretched up to 234 hours, and Taburet had to slow dosing of the drug to once every five to 10 days. With all patients she aimed for tacrolimus targets of 8 to 20 ng/mL from day 0 to week 6 and from 5 to 15 ng/mL afterwards.

Tacrolimus had no effect on antiretroviral pharmacokinetics, and everyone maintained a viral load below 50 copies/mL. The Bicêtre team concluded that managing tacrolimus-PI interactions is feasible with attentive monitoring.

Taburet did not report interactions between antiretrovirals and prednisone, but a study in healthy volunteers found that low-dose RTV jacks up exposure of prednison’s metabolite prednisolone in four days [abstract 14]. This study by Scott Penzak (US National Institutes of Health, Bethesda, Maryland) looked at 200 mg of RTV twice daily rather than the more frequently used 100-mg twice-daily dose.

Rifampin in combination with SQV/RTV-twice, even though some work suggests the toxicity arises only in people without HIV infection. 5

Hepatotoxicity with saquinavir/ritonavir plus rifampin

Earlier this year Roche Laboratories alerted clinicians to the risk of liver toxicity in people taking SQV/RTV with the TB drug rifampin (rifampicin). The startling result compelled Roche to contraindicate rifampin with SQV/RTV twice daily, even though some work suggests the toxicity arises only in people without HIV infection. 6

In people with HIV, on the other hand, cohort studies saw no toxic threat with the combination. 6

Roche Laboratories’ Malte Schutz detailed results of the 28-man study at the workshop [abstract 35]. Rifampin, a potent CYP3A4 inducer, trimmed expo-
Table 7. Possible mechanisms for lower paroxetine levels with FPV/RTV

<table>
<thead>
<tr>
<th>Possible mechanism</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine may have a secondary pathway through CYP3A4 when CYP2D6 is saturated.</td>
<td>Pro: Preliminary data suggest paroxetine inhibits CYP3A4 metabolism of pimozide; phenytoin reduces paroxetine exposure induction; FPV through CYP3A4 induces CYP3A4. Con: RTV inhibits CYP3A4, paroxetine does not interact with other CYP3A4 substrates (terfenadine, alprazolam).</td>
</tr>
<tr>
<td>FPV/RTV induces CYP2D6-mediated metabolism.</td>
<td>Pro: CYP2D6 is inducible, though conflicting data exist. Con: Rifampin only moderately induces CYP2D6 (24% to 30%); effect on paroxetine clearance is approximately 50%.</td>
</tr>
<tr>
<td>Displacement of protein binding</td>
<td>Would explain similar pharmacodynamic findings in the two study periods.</td>
</tr>
<tr>
<td>Effect on absorption</td>
<td>Would not explain the PI effect on paroxetine half-life.</td>
</tr>
</tbody>
</table>

Sure of unboosted SQV 70% in earlier work. Schutz and colleagues planned this trial in healthy volunteers to see if a 100-mg RTV boost would erase that deficit.

In a crossover design they randomized volunteers to take 1,000/100 mg of SQV/RTV twice daily or 600 mg of rifampin daily for 14 days. Then the PI group added rifampin and the rifampin group added the PIs.

Roche halted the trial before the crossover because the first nine men who added SQV/RTV to rifampin all had grade 3 or 4 transaminase elevations. At that point two of eight people in the other arm had grade 2 or 3 transaminase spurts. In the group that added the PIs after 14 days of rifampin, the transaminase jumps were dramatic, ranging from 12 to 70 times the upper limit of normal.

These changes came quickly. On day 14 everyone had rifampin or PI levels in the normal range. The liver enzyme leaps all happened in the next one to three days. One man in the group that added SQV/RTV to rifampin landed in the intensive care unit, but everyone regained normal liver function when treatment stopped.

The limited data that could be gathered before the study ended suggested that SQV/RTV slowed the breakdown of rifampin and its metabolite desacetyl-rifampin. That could account for the mounting transaminase readings, Schutz proposed.

The contraindication of rifampin with SQV/RTV comes as a keen blow to countries with a high prevalence of HIV/TB coinfection. Since clinicians usually try to control TB before attacking HIV, the apparently more dangerous rifampin-plus-PI sequence would be common.

Because this toxicity did not emerge in HIV-infected people combining rifampin with SQV/RTV—but only in healthy volunteers—some workshop attendees were reluctant to accept a permanent ban on combining these therapies. And Schutz said his company will not abandon study of the combination. Coincidentally, Argentine researchers found themselves in the midst of a rifampin/SQV/RTV trial—in people with HIV—when Roche Laboratories announced its results. Blood samples from that study are now analyzed.

Low paroxetine levels with fosamprenavir/ritonavir

Another shocker on a smaller scale came in a study combining fosamprenavir (FPV)/RTV with the antidepressant paroxetine [abstract 13]. One might expect RTV-boosted PIs to inhibit metabolism of drugs (like paroxetine) whose metabolism depends on CYP2D6, explained David Burger (Radboud University Nijmegen Medical Center). But expectation did not conform to reality in this study of 26 healthy volunteers, 18 of them women.

The crossover design called for half of the volunteers to take 20 mg of this selective serotonin reuptake inhibitor (SSRI) once daily for 10 days and for the other half to take it with 700/100 mg of FPV/RTV twice daily. After a 16-day washout, volunteers jumped to the alternate regimen for another 10 days.

Paroxetine did not affect levels of amprenavir (APV) or RTV, but the PIs sliced paroxetine’s AUC by 55%. The SSRI’s maximum concentration proved 51% lower with FPV/RTV than when given alone. Paroxetine’s half-life dwindled 25%.

What happened? Burger had a list of possibilities (Table 7).

Although this SSRI looks safe with FPV/RTV, Burger concluded, clinicians may have to raise its dose to achieve the desired antidepressant effect.

Dosing atazanavir with an H2 antagonist

Good absorption of atazanavir (ATV) depends on an acidic gastric stew, so drugs that quench stomach acid may lower levels of this PI. That’s just what happened in a study combining 40 mg of the proton pump inhibitor omeprazole with 300/100 mg of ATV/RTV once daily, and Bristol-Myers Squibb’s Sangeeta Agarwala suggested that the H2 antagonist famotidine and ATV can be taken safely with or without RTV [abstract 11]. But the studies involved healthy volunteers, whose gastric acidity differs from that of people with HIV infection.

In the first of two studies, 64 volunteers took either 400 mg of ATV in the morning or 400 mg in the evening for six days. Over the next week the morning-dose group added either (1) 40 mg of famotidine twice daily, (2) 40 mg of famotidine twice daily plus 8 ounces of cola, or (3) 40 mg of famotidine twice daily and 100 mg of RTV while trimming the ATV dose to 300 mg. The evening-dose group added 40 mg of famotidine, with the first famotidine dose taken 10 hours before ATV and the second two hours after ATV.

For people who took 400 mg of ATV in the morning, adding 40 mg of famotidine twice daily lowered ATV levels 40% to 50% compared with ATV alone. Quaffing a cola with the H2 blocker didn’t help. Compared with 400 mg of ATV in the
morning, 300/100 mg of ATV/RTV plus famotidine yielded a 79% higher ATV AUC, a 346% higher ATV trough, and an equivalent ATV peak. Separating the evening ATV dose from the two famotidine doses yielded ATV peaks and AUCs equivalent to those with ATV alone. In this arm the ATV trough with famotidine was 21% lower than with 400 mg of ATV alone.

The second protocol started with 300/100 mg of ATV/RTV in the morning for 10 days. Over the next 10 days the 48 volunteers added (1) 40 mg of famotidine twice daily, (2) 40 mg of famotidine twice daily plus 8 ounces of cola, or (3) 40 mg of famotidine twice daily plus an extra 100 mg of ATV.

Compared with ATV concentrations at the 300/100-mg dose, adding famotidine clipped the AUC 18%, the trough 28%, and the peak 14%. Adding famotidine with a cola chaser shaved ATV readings even more. The 400/100-mg dose plus famotidine yielded an ATV AUC and peak concentration similar to that attained with 300/100 mg without famotidine. The trough with 400/100 mg plus famotidine was 14% lower than with the 300/100-mg dose without famotidine.

Putting these pieces together, Bristol-Myers Squibb concluded that either (1) a 300/100-mg dose of ATV/RTV plus famotidine or (2) a 400-mg evening ATV dose 10 hours after the morning famotidine and two hours before the evening famotidine yields ATV levels equivalent to those reached with 400 mg once daily. Most clinicians probably hope for the ATV exposure that they get with RTV-boosted 300/100 mg once daily. To reach those levels with famotidine, the ATV/RTV dose should be 400/100 mg.

### Combining atazanavir with lopinavir/ritonavir

A study of 28 heavily pretreated people switching to standard doses of ATV plus LPV/RTV (and other antiretrovirals) found adequate levels of both boosted PIs after an average 29 weeks of follow-up [abstract 56, poster 4.10]. Fasting lipids and bilirubin rose slightly.

Michael Zilly (University of Würzburg, Germany) and colleagues checked 171 plasma PI levels, planning to raise doses if they saw consecutive LPV troughs below 3,500 ng/mL or consecutive ATV troughs below 250 ng/mL. They never did. In fact they cut the LPV dose in two people with high troughs and nagging diarrhea.

The median LPV trough measured 4,472 ± 2,226 ng/mL and the median ATV trough 695 ± 450 ng/mL. Lopinavir levels never fell under 1,400 ng/mL and ATV levels never dipped under 150 ng/mL. Both drugs peaked four hours after dosing at a median 10,201 ± 3,472 ng/mL for LPV and 2,544 ± 638 ng/mL for ATV. Zilly rated virologic suppression “adequate” but did not define responses.

A 12-person study presented at this year’s European HIV Drug Resistance Workshop charted higher LPV levels with ATV/RTV reached a similar conclusion: ATV. Zilly rated virologic suppression “adequate” but did not define responses.

### Impact of hepatitis on fosamprenavir or lopinavir

Hepatitis virus-coinfected people with cirrhosis had higher APV levels than coinfected people with chronic hepatitis or people infected only with HIV in a study reported by Elena Seminari (San Raffaele Scientific Institute, Milan) [abstract 66, poster 5.8]. She ran two analyses of APV exposure in people taking 700/100 mg of FPV/RTV twice daily in an expanded access program.

The first study involved 15 controls infected only with HIV, 12 coinfected people with chronic hepatitis (10 with HCV and two with hepatitis B virus [HBV]), and six coinfected people with histologically or clinically diagnosed cirrhosis (all with HCV).

Amprenavir troughs measured before the morning dose of FPV/RTV averaged 2,066 ng/mL in controls, 1,431 ng/mL in the chronic hepatitis group, and 4,678 ng/mL in the cirrhotic group. The geometric mean ratio for troughs was 1.90 (95% CI 1.07 to 3.01) when comparing the cirrhotic group with controls and 2.46 (95% CI 1.9 to 4.58) when comparing the cirrhotic group with the chronic hepatitis group.

Seminari also collected blood samples over 12 hours in 14 men — six controls, four with chronic hepatitis, and four with cirrhosis. Again the group with cirrhosis had substantially higher APV exposure than the other two groups (Table 8).

A second observational study of coinfected people taking standard-dose LPV/RTV reached a similar conclusion: José Moltó (Germans Trias i Pujol University Hospital, Badalona, Spain) found that HCV barely upset LPV levels in coinfected people without impaired liver function [abstract 36].

This analysis involved 22 coinfected people with a Child-Pugh score below 6 and 18 people infected only with HIV.

### Table 8. APV exposure with FPV/RTV 700/100 mg twice daily

<table>
<thead>
<tr>
<th>Trough (ng/mL)</th>
<th>Peak (ng/mL)</th>
<th>T_{max} (h)</th>
<th>AUC0-12h (ng•h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 6)</td>
<td>2,646</td>
<td>5,582</td>
<td>3.5</td>
</tr>
<tr>
<td>Chronic hepatitis (n = 4)</td>
<td>1,536</td>
<td>4,587</td>
<td>2.5</td>
</tr>
<tr>
<td>Cirrhosis (n = 4)</td>
<td>3,979</td>
<td>9,193</td>
<td>1.5</td>
</tr>
</tbody>
</table>

AUC0-12h = area under the concentration-time curve over 12 hours.

### Table 9. Mean LPV exposure in people with or without HCV

<table>
<thead>
<tr>
<th>HIV+/HCV+</th>
<th>HIV+/HCV-</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-12h (mg•h/L)</td>
<td>93.4</td>
<td>83.0</td>
</tr>
<tr>
<td>Trough (mg/L)</td>
<td>7.67</td>
<td>6.66</td>
</tr>
<tr>
<td>Clearance (L/h)</td>
<td>4.55</td>
<td>5.55</td>
</tr>
<tr>
<td>Apparent volume of distribution (L)</td>
<td>69.17</td>
<td>57.25</td>
</tr>
</tbody>
</table>

Tmax = time to maximum concentration.
Everyone had taken standard-dose LPV/RTV for at least four weeks. The groups compared well in age and weight. As one would expect, the HCV group had higher levels of aspartate aminotransferase (53.5 U/L versus 23.0 U/L) and alanine aminotransferase (56.0 U/L versus 23.0 U/L). Measuring LPV levels at steady state, Moltó found no significant differences in mean values between the two groups (Table 9).

Ritonavir troughs did prove significantly higher in the coinfected group (1.12 versus 0.67 mg/L, \( P = 0.027 \)), and Moltó saw a trend toward higher RTV AUC (6.90 versus 4.82 mg•h/L/L) in the people with HCV (\( P = 0.067 \)). But these higher levels apparently had only a modest impact on LPV. Gender, age, body mass index, and transaminase readings did not affect LPV pharmacokinetics.

Workshop attendees observed that studies like these may suffer from selection bias: Coinfected people whose PI levels climb quickly may stop their protease drugs before they can be selected for study.

<table>
<thead>
<tr>
<th>Trough (ng/mL)</th>
<th>Response (%)*</th>
<th>Total bilirubin &gt;2.5 mg/dL (%)</th>
<th>Unconjugated bilirubin &gt;2.0 mg/dL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150 (( n = 12 ))</td>
<td>58.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>150 to 850 (( n = 20 ))</td>
<td>75</td>
<td>16.6</td>
<td>12.5</td>
</tr>
<tr>
<td>&gt;850 (( n = 13 ))</td>
<td>100</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

*Fewer than 50 copies/mL or more than a 2-log drop in viral load.

![PROTEASE INHIBITOR RESPONSE AND SIDE EFFECTS](image)

Atazanavir has won the interest of pharmacologists curious to define its therapeutic range and to predict how people will respond to it. Other PI research presented at the workshop involved potential links between LPV levels and lofty lipids.

**Defining atazanavir’s therapeutic range**

Stefano Bonora (University of Turin, Italy) confirmed his preliminary finding that the therapeutic range of ATV stretches from 150 to 850 ng/mL [abstract 60]. Bonora’s analysis involved 51 people, 34 of them men, enrolled in an ATV expanded access program. Eleven already had a viral load below 50 copies/mL; in the others median viremia stood at 3.5 logs (interquartile range [IQR] 1.79 to 4.9 logs). Seventeen people had never tried a PI, and the median number of previous PIs was 1 (range 0 to 6). Thirty people (59%) started ATV/RTV (300/100 mg).

Defining virologic response as fewer than 50 copies/mL or more than a 2-log drop in viral load, Bonora counted 40 responders among 50 people at week 12 (80%) and 34 among 45 people at week 24 (75.5%). At week 24 the ATV trough averaged 208 ng/mL among people taking unboosted ATV and 1,046 ng/mL among those getting a lift from RTV.

Comparing 35 week-24 responders and 10 nonresponders, Bonora found three significant differences:

- Baseline viral load: 2.5 log in responders versus 4.6 log (\( P = 0.008 \))
- Previous PIs: One in responders versus three (\( P = 0.013 \))
- ATV trough: 834 ng/mL in responders versus 191 ng/mL (\( P = 0.006 \))
- Genotypic inhibitory quotient (GIQ) (trough/number of PI mutations): 330 in responders versus 5.8 (\( P = 0.019 \)).

A GIQ based on ATV-specific mutations did not significantly discriminate responders from nonresponders (412 versus 7, \( P = 0.08 \)).

Among people with a trough above 150 ng/mL, 81% had a 24-week virologic response, versus 37.5% with a trough below that cutoff (\( P = 0.027 \)). As a response predictor a trough above 150 ng/mL had 88% sensitivity but only 50% specificity. People with a trough under 150 ng/mL had a 4.1 times higher risk of failure.

Among people with a PI-based GIQ above 100, 88.8% had a virologic response at 24 weeks versus 33.3% with a GIQ under 100 (\( P = 0.006 \)). A GIQ of 100 had 89.5% sensitivity and 85.7% specificity in predicting response. People whose GIQ languished below 100 had a 4.7 times higher risk of failure.

Foraging for the high end of the therapeutic range, Bonora found that an ATV trough atop 850 ng/mL predicted total bilirubin readings above 2.5 mg/dL with 60% sensitivity and 78% specificity. The same trough predicted an unconjugated bilirubin of 2.0 mg/dL with 66.7% sensitivity and 78.6% specificity.

Among study participants whose ATV trough fell within the 150- to 850-ng/mL target range, 75% had a virologic response and 17% had elevated bilirubin (Table 10). Although everyone with a trough above 850 ng/mL responded, 40% of them had high bilirubin.

Bonora concluded that 150 to 850 ng/mL represents a reliable therapeutic range for ATV. But a Bristol-Myers Squibb representative wondered whether clinicians would sacrifice too many responses with a top trough cutoff of 850 ng/mL. Everyone with a trough above that mark responded virologically. Although 40% of them had high bilirubins, the Bristol-Myers Squibb representative argued, some may see that as only a “cosmetic” side effect. Only two people in Bonora’s group stopped ATV because of hyperbilirubinemia.

**Genotypic inhibitory quotient predicts response to atazanavir**

Bruno Lacarelle (Timone Hospital, Marseille, France) also found that GIQ predicts virologic response to ATV [abstract 1]. But unlike Bonora he determined that both a GIQ based on ATV-specific mutations and a GIQ based on all protease mutations predicted response. The different result may reflect (1) disparate response definitions, (2) more RTV boosting in Lacarelle’s cohort, and (3) the different populations studied: More people in Lacarelle’s group had PI experience. Lacarelle’s findings also differed from Bonora’s in that he could not define a trough cutoff that predicted response.
The Marseille cohort included 35 people with treatment experience and one naive to antiretrovirals. While 32 took RTV-boosted ATV, four took the unboosted PI. The group had tried a median of two PIs (range zero to five). They had a median of three (range zero to 15) PI mutations and one (zero to 10) ATV-related mutation.

After two months of treatment 26 people (72%) had a virologic response, defined as a viral load below 400 copies/mL or at least a 1-log drop in viremia. Atazanavir trough and a GIQ based on all protease mutations did not predict the month-3 response, but number of PI mutations, number of ATV-specific mutations, GIQ based on ATV mutations, and CD4 gain did correlate with response (Table 11).

In a multivariate analysis ATV trough, PI mutations, and ATV-specific mutations did not predict response, but both the PI mutation-based GIQ and the ATV mutation-based GIQ did. Lacarelle reckoned the ATV GIQ response cutoff at 2.3 because 25% of people with a GIQ under 2.3 responded versus 75% with a higher GIQ (P = 0.014).

Yet in a study presented earlier this year, Bonora’s colleague Daniel Gonzalez de Requena set a PI-based GIQ cutoff at 60.8 Lacarelle explained that the wide difference between that result and his reflects the log transformation of his GIQ calculation. One attendee observed that if HIV pharmacologists expect clinicians to start using GIQ, they will have to agree on methods.

Who needs 300/200 or 400/200 mg of atazanavir/ritonavir?

Authorities in British Columbia recommend the 300/100-mg dose of ATV/RTV—and TDM—for everyone starting this once-daily PI. But do some people need even higher doses?

To find out, Chris Alexander (University of British Columbia) sorted TDM records of people starting ATV/RTV between September 2003 and December 2004 [abstract 91, poster 8.3]. Alexander found that 34 people (25%) had a PI dose adjustment. As a result the Vancouver team made 42 pairwise comparisons:

- 28 switches from 300/100 to 300/200 mg once daily
- 6 switches from 300/200 to 400/200 mg once daily
- 8 switches from 300/100 to 400/200 mg once daily

Looking at steady-state ATV and RTV levels in people not changing other antiretrovirals around sampling time, Alexander found that the first 28 dose changes bolstered the percentage of people with a detectable RTV level (> 80 ng/mL) from 21% to 58% (P < 0.01). The eight switches from 300/100 to 400/200 mg lifted the percentage of people with a detectable RTV level from 12.5% to 75% (P < 0.01). Although 35% of study participants also had at least a 30% jump in their ATV trough with the dose adjustment, overall ATV exposure did not climb significantly.

The British Columbia team concluded that the recommended 300/100-mg dose yields adequate ATV concentrations for most people. While raising the dose to 300/200 mg once daily improves ATV exposure in a subset of people, the 400/200-mg dose “may more reliably increase ATV levels without further increasing the cost.”

Lopinavir trough tied to high lipids

Research to date disagrees on whether high LPV exposure correlates with higher lipid and glucose levels.9–12 The latest look at this question, a retrospective analysis involving 20 people, found that LPV troughs above 7 mg/L correlated with a 35% triglyceride spurt. In comparison eight people with a trough between 3 and 7 mg/L averaged a 22% gain in cholesterol and a 35% triglyceride spurt.

Table 11. ATV response predictors in treatment-experienced people

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Nonresponders</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median trough (ng/mL) (range)</td>
<td>593 (15 to 1,480)</td>
<td>992 (50 to 1504)</td>
<td>0.14</td>
</tr>
<tr>
<td>Median PI mutations (range)</td>
<td>3 (0 to 8)</td>
<td>7.5 (1 to 15)</td>
<td>0.001</td>
</tr>
<tr>
<td>Median ATV mutations (range)</td>
<td>1 (0 to 4)</td>
<td>5 (1 to 10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total GIQ</td>
<td>2.35 (1 to 2.9)</td>
<td>1.99 (1.56 to 2.62)</td>
<td>0.39</td>
</tr>
<tr>
<td>ATV GIQ</td>
<td>2.66 (1.7 to 2.92)</td>
<td>2.10 (1.7 to 2.93)</td>
<td>0.07</td>
</tr>
<tr>
<td>CD4 change (cells/mm³)</td>
<td>+66 (-66 to +451)</td>
<td>+3 (-82 to +131)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Tenoforv, didanosine, and protease inhibitors

Tenoforv has had its ups and downs since winning approval as an antiretroviral nucleotide analog. No one doubts the potency or convenience of this once-daily pill, now combined in a single tablet with FTC and perhaps soon with FTC and EFV as a once-daily troika. Tenoforv boasts a handsome short-term toxicity profile, though its long-term impact on kidneys13 and bones14 may prove more problematic.

But the worst news about TDF came from studies of people taking it with two other purine analogs—didanosine (ddI) and abacavir (ABC). In a cohort coupling TDF with 400 mg of ddI, more than half of 302 people lost more than 100 CD4 cells/mm³ over 48 weeks, and a third lost more than 200 cells/mm³—even though they responded virologically.15 Tenoforv combined with ddI, ABC, and/or lamivudine (3TC)—without a PI or NNRTI—fell far short virologically in a spate of studies.16–20
When TDF plus ddl also flopped virologically in people starting it with EFV,\textsuperscript{21-23} the drugs’ two makers warned European clinicians away from combining TDF and ddl.\textsuperscript{24} At the 6th International Workshop on Clinical Pharmacology of HIV Therapy, Giovanni Di Perri (University of Torino, Italy) wondered why regulators had not banned TDF/ddI combinations from the start, since both drugs compete for adenosine in binding to reverse transcriptase. But he admitted he overlooked that inconvenience fact and prescribed the twosome to look harder at NRTI effects in different cell subsets, though no one calls that assignment easy. Only eight of 98 workshop studies (8%), for example, sized up intracellular quotients of NRTI triphosphates. But Séverine Compain (SPIBO/CEA Salay, Gif-sur-Yvette, France) did propose a method for measuring triphosphates in different cell populations (combined high-performance liquid chromatography and tandem mass spectrometry) [abstract 68, poster 5.15].

Much head scratching fostered some hypothesizing on the internecine nuances between TDF and other reverse transcriptase inhibitors. The workshop’s keynote speaker, Daniel Kuritzkes (Harvard Medical School, Boston), proposed that certain nucleosides (-tides) team up to stifle evolution of resistant virus, while other combinations appear to promote resistance (Table 13).

Notably, TDF/3TC turns up in both columns of this table—and no one knows why. In lab dishes TDF handcuffs the 3TC- and FTC-resistant M184V mutant. Yet in trials that combined TDF and 3TC with ABC in treatment-naive people, M184V arose and the regimen crashed.\textsuperscript{16,17}

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One way to explain this seeming antinomy, Kuritzkes proposed, may be that different resistance mutations can emerge from different cellular compartments, as happened in the GlaxoSmithKline study of TDF, 3TC, and ABC.\textsuperscript{16,25}

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Late in 2004 Thomas Kakuda (Roche Laboratories) and colleagues proposed that both the CD4 decays with TDF/ddI and the antiviral frangibility of TDF/ddI/ABC rest in TDF’s inhibition of purine nucleoside phosphorylase (PNP).\textsuperscript{26} Because PNP breaks down naturally occurring purines, thwarting PNP would promote purine pileups—especially deoxyadenosine triphosphate (dATP) or deoxyguanosine triphosphate (dTTP). That could do two things, Kakuda explains:

- Foster T-lymphocyte deficits similar to those seen with genetic PNP deficiency
- Upset the ratio of deoxyribonucleotide triphosphates to purine analog phosphates and so favor incorporation of deoxyribonucleotide triphosphate by reverse transcriptase over incorporation of adenosine or guanosine NRTI triphosphates (ddl or ABC respectively)

The second effect would enfeeble purine analogs like ddl and ABC when combined with TDF.

Kakuda suggests clinicians may want to limit TDF’s nucleoside teammates to the purine analogs zidovudine (AZT), d4T, 3TC, and FTC. But that may not be a failsafe strategy, according to one workshop report:

\textbf{Hypotheses explaining tenofovir/nucleoside reverse transcriptase inhibitor failures}

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Kakuda suggests clinicians may want to limit TDF’s nucleoside teammates to the pyrimidine analogs zidovudine (AZT), d4T, 3TC, and FTC. But that may not be a failsafe strategy, according to one workshop report:

\textbf{CD4 shortfalls with tenofovir without didanosine}

At this year’s workshop, Andrew Luber (University of Pennsylvania, Philadelphia) extended Kakuda’s hypothesis, suggesting that CD4s may also tumble in people taking TDF without ddl—though five of nine people studied took TDF with ABC [abstract 53, poster 4.7].

Luber looked at CD4 changes in seven men and two women who had at least two consecutive RNA readings below 400 copies/mL yet lost CD4 cells on at least two measures separated by at least two months. He eliminated anyone who might have T-cell deficits due to other drugs or illnesses. The regimens involved a PI boosted by RTV in five people, quadruple NRTIs in two, triple NRTIs in one, and TDF plus ABC and NVP in one.

These nine people had taken their current combination for a median of 21 months (range six to 40 months). Over a median of 11 months (range four to 25 months), their CD4 counts plunged by a median 297 cells/mm\(^3\) (range 88 to 615 cells/mm\(^3\)).

What explains these CD4 drops in people taking TDF without ddl? For the five people also taking ABC, Luber invoked Kakuda’s hypothesis that TDF-provoked purine spirals could tax the ability of ABC’s triphosphate to bind to reverse transcriptase. But that would not explain why ABC apparently worked well virologically in these people.

For the five people taking TDF with a boosted PI, Luber observed that low-dose RTV may inhibit expression of the drug transporter multidrug-resistance protein 4 (MRP4) on T cells. That would favor intracellular stockpiling of TDF’s active metabolite. And more intracellular TDF

<table>
<thead>
<tr>
<th>Glucose (mmol/L)</th>
<th>Baseline</th>
<th>Month 1</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5 ± 1.4</td>
<td>4.9 ± 0.8</td>
<td>5.0 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.4 ± 1.4</td>
<td>2.8 ± 1.5</td>
<td>2.8 ± 2.1</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>4.7 ± 1.6</td>
<td>5.8 ± 1.2*</td>
<td>5.8 ± 1.5*</td>
</tr>
</tbody>
</table>

*\(P = 0.034 \) versus baseline.
\(SD = \) standard deviation.

<table>
<thead>
<tr>
<th>NRTI combinations and evolution of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impede resistance</td>
</tr>
<tr>
<td>• AZT/ddI</td>
</tr>
<tr>
<td>• AZT/ABC</td>
</tr>
<tr>
<td>• AZT/3TC</td>
</tr>
<tr>
<td>• (TDF/FTC?)</td>
</tr>
</tbody>
</table>

\(\text{Table 12. Mean lipid and glucose changes (+ SD) through six months of LPV}\)

\(\text{Table 13. NRTI combinations and evolution of resistance}\)
would mean more PNP inhibition—the mechanism Kakuda elects to explain CD4 ebb.

As Luber cautions, an uncontrolled analysis like this cannot eliminate other possible explanations of CD4 swoons in people taking TDF without ddI. Perhaps natural variability in CD4 tallies accounts for these nine cases; only three of them also had drops in CD4 percent. Or CD4 slumps could occur as often with non-TDF regimens but go unreported in trials—a few downturns after that.

Tenoforvir intracellular half-life at least one week

Tenoforvir’s active metabolite lingers in PBMCs for more than a week after people stop the drug, according to results of a study by Jacques Grassi (CEA, Gif-sur-Yvette, France) [abstract 20, poster 2.13]. The analysis, published just after the workshop,27 involved eight people taking TDF without ddI, 16 taking 400 mg of ddI daily without TDF, and 14 taking TDF plus ddI at 250 mg daily. A longitudinal substudy assessed intracellular TDF and ddI levels in three people quitting TDF and raising their ddI dose from 250 to 400 mg daily.

Comparing people taking each drug alone with those combining the NRTIs, Grassi found no difference in intracellular concentrations of the active metabolites:

- ddI with TDF 5.06 fmol/10⁶ cells versus ddI without TDF 6.70 fmol/10⁶ cells ($P = 0.17$)
- TDF with ddI 134.5 fmol/10⁶ cells versus TDF without ddI 158.4 fmol/10⁶ cells ($P = 0.152$)

Neither did Grassi see significant variation between intracellular TDF readings from one TDF dose to the next. But TDF’s active diphosphate metabolite could be measured for three weeks in all three people who stopped the nucleotide analog. Grassi figured the intracellular half-life at 7.5 days.

Tenoforvir’s perdurable intracellular half-life probably helps explain the drug’s potency. But it also poses a risk of resistance if people stop TDF along with all other drugs in their regimen, or if they stop TDF and continue a poorly suppressive regimen. That would allow HIV to replicate in the face of dwindling—but persistent—TDF levels.

Because neither plasma nor intracellular NRTI half-lives predict responses to regimens containing these drugs, Trevor Scott and GlaxoSmithKline colleagues explored a new inhibitory quotient—the intracellular inhibitory quotient (IIQ) [abstract 7, poster 1.7]. As with the traditional IQ and the GIQ, a higher IIQ should mean a better response because it accounts for both drug exposure (usually measured as a trough) and viral susceptibility.

Scott tried two IIQ formulas:

\[ \text{IIQ} = \frac{\text{Intracellular NRTI tri- or diphosphate trough/50\% inhibitory concentration (IC}_{50})}{\text{Ki}} \]

\[ \text{IIQ} = \frac{\text{Intracellular NRTI tri- or diphosphate trough/Ki}}{\text{IC}_{50}} \]

Ki is the concentration of NRTI needed to overcome competition by endogenous triphosphate for incorporation into cellular DNA by HIV reverse transcriptase.

With either equation the 24-hour IIQ for ABC easily topped the IIQs for TDF or d4T, with IC₅₀ for ABC easily topping the IIQ of TDF.

Table 14. Intercostal variability in NRTI absorption, clearance, and distribution

<table>
<thead>
<tr>
<th>NRTI</th>
<th>Oral clearance</th>
<th>Volume of distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC</td>
<td>62%</td>
<td>49%</td>
</tr>
<tr>
<td>d4T</td>
<td>77%</td>
<td>82%</td>
</tr>
<tr>
<td>AZT</td>
<td>49%</td>
<td>88%</td>
</tr>
</tbody>
</table>

*Zero-order absorption figured as duration of absorption.

New data on atazanavir/ritonavir with tenoforvir

Earlier studies disagree on whether TDF lowers levels of ATV. Two studies recorded
lower ATV troughs with TDF, whether ATV got the RTV boost or not. But a cross-sectional study of 79 people found no ATV trough difference in people taking the RTV-boosted PI with or without TDF. At this year’s workshop, Sangeeta Agarwala and Bristol-Myers Squibb colleagues offered data confirming reasonable ATV exposure with simultaneous TDF and ATV/RTV at 300/100 mg [abstract 16, poster 2.9].

The study involved 28 healthy adults, 18 of them men and 10 women. For 10 days they took 300 mg of TDF daily. After a washout everyone took 300/100 mg of ATV/RTV in the morning for 10 days followed by either:

- 400/100 mg ATV/RTV plus 300 mg TDF simultaneously in the morning for 10 days
- 300/100 mg of ATV/RTV in the morning and 300 mg of TDF in the evening for 10 days

Atazanavir’s AUC proved 38% higher with the 400/100-mg dose plus TDF than with the 300/100-mg dose without TDF. The PI’s peak concentration was 31% higher with 400/100 mg plus TDF than with 300/100 mg alone. Tenofovir’s AUC was 55% higher and its peak 39% higher with 400/100 mg of ATV/RTV than without the PIs. Because of the higher exposure of both drugs, Bristol-Myers Squibb does not recommend 400/100 mg of ATV/RTV with TDF.

Tenofovir had practically no impact on APV levels with either dose. With the 1,400/100-mg dose, APV’s trough was 24% higher with TDF than without it, a nonsignificant difference. With the 1,400/200-mg dose, APV’s peak was 11% higher with TDF than without it.

Tenofovir monophosphate levels differed little in men taking 1,400/100 mg of FPV/RTV versus those taking 1,400/200 mg. Tenofovir’s AUC and maximum concentration were slightly lower with 1,400/200 mg, and the trough was slightly higher with the 1,400/200-mg dose.

Three people dropped out of the study, two with skin reactions and one with gastrointestinal intolerance. Kurowski concluded that no dose modifications are needed when combining FPV/RTV with TDF.

Gilles Peytavin (Bichat-Claude Bernard Hospital, Paris) looked for potential interactions between twice-daily 700/100-mg FPV/RTV and once-daily TDF in 21 people with HIV infection [abstract 32, poster 2.25]. All of these treatment-experienced people had taken boosted FPV with TDF and another NRTI for at least one month. None were taking an NNRTI or a second PI. Peytavin measured APV, RTV, and TDF levels once in each of these 14 men and seven women and genotyped virus for resistance mutations.

The study group had a median viral load of 3.79 log (range 2.30 to 6.12 log); four people (19%) had a viral load below 200 copies/mL. The median CD4 count was 174 cells/mm³ (range 2 to 497 cells/mm³). Genotyping spotted a median of two major protease mutations (range zero to four).
After one to two months of FPV/RTV, the median viral load measured 2.37 log and nine people had fewer than 200 copies/mL. Seven others had at least a 1-log drop in viral load. The median CD4 count climbed to 224 cells/mm³.

Only three people had a minimum APV concentration below 1,250 ng/mL—the cutoff for a 10-fold drop in viral load at 12 weeks in the Genophar pharmacologic substudy of TDF plus 600/100 mg of APV/RTV twice daily. No one had an unmeasurable APV level. The median APV trough, 1,586 ng/mL, compared well with the median trough among 98 people in the Genophar study. Intertient variability in APV troughs was about 37%.

The median 24-hour TDF plasma concentration measured 48 ng/mL, close to the 44 ng/mL in a study of TDF with FPV/RTV. Intertient variability in TDF levels was about 55%.

With this twice-daily dose of FPV/RTV, Peytavin confirmed Kurowski's once-daily finding of no clinically meaningful interaction between TDF and the boosted PI.

### ENTRY INHIBITORS AND NNRTIs

Enfuvirtide (ENF) remains the only antiretroviral that keeps HIV out of T cells, but others are racing toward approval. CCR5 antagonists have reached crucial clinical trial stages, and one has even forsaken its faceless number for a name. This year's workshop had news on ENF, CCR5 candidates, and two new drugs from a more familiar class, the NNRTIs.

**An easier way to take enfuvirtide?**

Despite its niche as the only antiretroviral that frustrates fusion, ENF has its drawbacks. Besides its high price, the twice-daily needles make it intolerable to some people and painful to most. Nothing seems likely to solve the first problem, but a transdermal gas pressure-powered injector could solve the second. Marianne Harris (British Columbia Centre for Excellence in HIV/AIDS, Vancouver) offered details of a 23-person trial in which people taking ENF by needle switched to the Biojector system [abstract 48].

Nurses find it easier to teach people to use Biojector than to use needles, according to Harris. And because people can wield the device with one hand, they can reach more body sites to inject. The transdermal injector causes less pain and less tissue trauma than the ENF needle.

The Vancouver team measured ENF levels 11 to 13 hours after dosing before people switched to Biojector and during a new four weeks of treatment with the new device. Enfuvirtide troughs and peaks proved equivalent with the skin-skimming injector and the needle, while a 0-to-31 injection site reaction score dropped after the switch to Biojector (Table 15).

No one who started using Biojector with a viral load below 50 copies/mL had a rebound, and viral loads dropped in people with detectable loads when they switched to the no-needle jet.

Charles Flexner (Johns Hopkins University, Baltimore) observed that ENF troughs ranged lower with Biojector than with the needle, and that will have to be watched in bigger trials. In the United States, others observed, the FDA would probably not approve such a device for ENF without first testing it in healthy volunteers. Biojector is not the only gas pressure-powered injector currently being tested.

### Enfuvirtide level predicts early virologic response

A small study of people starting ENF as part of a salvage regimen linked the drug's week-2 AUC with viral load drops at week 4 [abstract 71, poster 5.10]. This study by Stefano Bonora (University of Turin, Italy) also yielded an ENF trough cutoff that predicts the week-12 response.

The 38 study participants all started ENF with one or two boosted PIs and two or three NRTIs. Seven (18%) also started an NNRTI. This group had advanced HIV infection, with a median viral load of 5.16 log (IQR 4.7 to 5.5 log) and a median CD4 count of 49 cells/mm³ (IQR 19 to 109 cells/mm³).

Median viral load dropped 0.58 log at week 4 and 0.41 log at week 12. Enfuvirtide's week-2 AUC, peak, and trough (± standard deviation) measured 45,633 ± 16,239 ng·h/mL, 5,041 ± 1,657 ng/mL, and 2,318 ± 1,245 ng/mL. Linear regression analysis isolated three factors that predicted viral load dips at week 4:

- Number of active drugs in background regimen (P=0.026)
- LPV as an active drug (P=0.0034)
- ENF AUC at two weeks (P=0.0086)

Only the number of active drugs in the regimen predicted viral load drops at week 12. At that point 15% had a viral load below 50 copies/mL. Logistic regression analysis again picked out number of active drugs as a predictor of a week-12 sub-50 load (P=0.04). The sub-50 predictive power of ENF trough at week 12 fell short of statistical significance (P=0.07).

Bonora determined that an ENF trough above 2,200 ng/mL predicted a 12-week load below 50 copies/mL with a sensitivity of 100% and a specificity of 62.5%.

### GlaxoSmithKline CCR5 antagonist and CYP enzymes

GlaxoSmithKline's CCR5 frustrator, labeled 873140, inhibits CYP3A4, the isoenzyme famous for metabolizing PIs. The CCR5 drug is also a weak inhibitor of CYP2C9 and a modest inhibitor of CYP2C19.

To gauge potential CYP inhibition more closely, Ivy Song (GlaxoSmithKline) recruited 15 healthy volunteers to quaff a cocktail of caffeine, warfarin, omeprazole, dextromethorphan, and midazolam—probes used to reckon interactions with (respectively) CYP1A2, CYP2C9, CYP2C19,
CYP2D6, and CYP3A4 [abstract 75]. Later, everyone took 40 mg of 873140 every 12 hours for seven days, then swallowed the probe brew again.

Figuring drug to no-drug ratios, Song saw the greatest potential interaction with CYP3A4, which she labeled “weak inhibition” (Table 16).

Although Song maintained that the CYP3A4 inhibition she measured would have little clinical relevance, some pharmacologists in the audience were not so sure. Especially if GlaxoSmithKline ends up seeking approval for a higher dose of their CCR5 drug, they worried that Song’s numbers may augur higher PI levels in people taking 873140.

**Proposed dose adjustments with maraviroc**

Pfizer’s CCR5 antagonist—formerly tagged UK-427,857 but newly christened maraviroc (muh-RAV-eh-rok)—neither inhibits nor induces CYP3A4. But it is a CYP3A4 substrate, so drugs that inhibit CYP3A4 (PIs, ketoconazole) could raise maraviroc levels and drugs that induce CYP3A4 (EFV, rifampin) could lower them.

That’s what happened in a batch of studies reviewed by Pfizer’s Gary Muirhead [abstract 76]. Ketoconazole, SQV, ATV, and ATV/RTV inflated maraviroc’s minimum concentration two to three times and its AUC four to five times. Efavirenz lowered maraviroc’s maximum concentration and AUC by about 50% and rifampin lowered it by 70%. Efavirenz also cut the CCR5 antagonist’s exposure when given with PIs, but CYP3A4 inhibition by PIs yielded a net gain in maraviroc exposure.

GlaxoSmithKline believes maraviroc’s 100-mg twice-daily dose will have to be halved when the drug teams up with PIs. When given with EFV (without PIs), maraviroc’s dose will probably need doubling.

In a separate study using a single 300-mg dose of maraviroc, Muirhead confirmed the effects of EFV and LPV/RTV on maraviroc exposure [abstract 31, poster 2.19]. Nevirapine boosted maraviroc’s peak slightly but had no effect on its AUC.

**New data on Tibotec’s TMC nonnucleoside reverse transcriptase inhibitors**

Tibotec has two candidates in the running as “next-generation” NNRTIs, TMC125 and TMC278. Both neatly corral wild-type virus and pen up certain NNRTI-resistant strains. Although TMC125 leads TMC278 in development, TMC278 has the advantage of once-daily dosing and looks potent at a range of doses studied so far.36 But work on both drugs continues.

One problem with the elder candidate, TMC125, is poor oral bioavailability with the tested formulation. Trying to squeeze more drug into fewer pills, Tibotec’s Monika Schöller compared four new formulations with the current tablet in 45 healthy volunteers in a randomized trial of TDM failed to prove that this strategy improves treatment outcome or shields people from antiretroviral side effects. Yet a separate cross-sectional study determined that nearly one quarter of PI and NNRTI levels in a clinic cohort lay outside the therapeutic range. And a database analysis challenged conventional wisdom in suggesting that twice-daily therapy has a distinct advantage over once-daily dosing.

**Is therapeutic drug monitoring worth the effort?**

Measuring highly variable antiretroviral levels in highly variable individuals seems to make eminent sense. But no one has nailed down the virologic or safety value of TDM.
Reviewing results of POPIN—a 122-person randomized TDM trial—Saye Khoo (University of Liverpool) maintained that previous TDM trials have proved “persuasive rather than conclusive” [abstract 59]. And studies of adherence support—another element of POPIN—so far fail to show sustained benefit. Although national treatment guidelines advocate TDM for certain people with HIV, Khoo noted, none supports the strategy for routine use in unselected individuals.

POPIN randomized 45 people taking PIs and 89 taking NNRTIs to standard of care monitoring or TDM plus adherence support. All study participants had pushed their viral load below 50 copies/mL for more than six months or were starting or switching to a new PI or NNRTI regimen.

TDM consisted of trough measures and two-hour postdose sampling at baseline and every 12 weeks in people with a sub-50-copy load and at weeks 2, 4, 12, then every 12 weeks in people starting or switching to a new regimen. Nurses used a structured questionnaire to encourage adherence. Everyone also kept a TDM diary and got food advice.

POPIN had three primary endpoints:

• Viral load not below 50 copies/mL 24 weeks after starting or switching
• Viral load rebound above 50 copies/mL
• Treatment-limiting toxicity

The analysis included 85 people in the sub-50 group and 37 in the start/switch group. Khoo and colleagues randomized 63 to TDM and 59 to standard of care. The researchers recorded a marginally higher CD4 count in the standard-of-care group (430 cells/mm$^3$) than in the TDM group (280 cells/mm$^3$) ($P=0.06$). Median follow-up measured 72 weeks and ranged from six to 172 weeks.

At the end of follow-up only 19 people met one of the failure criteria, with no difference between the TDM and standard-of-care groups in either a switch-equals-failure analysis or a switch-censored analysis. Neither did the groups differ in toxicity rates, CD4 count change, or proportions reaching an RNA reading below 400 copies/mL. Risk of failure at 96 weeks, based on 427 drug levels in 108 people, measured 40% in the TDM group and 32% in the standard-of-care group.

Interindividual variation in EFV, NVP, and LPV levels proved high, while intraindividual variation was somewhat lower (Table 17).

One reason researchers have a hard time proving TDM benefits may be poor adherence — by physicians. Among 20 POPIN participants with repeatedly high or low drug levels, physicians of only seven (35%) followed dose-switch advice. The earlier ATHENA study charted 50% physician adherence among 57% of those who answered a questionnaire.

These low adherence rates do not necessarily signal negligence, Khoo suggested. If a person has a drug level above the therapeutic range—yet shows no hint of toxicity and has HIV under wraps—physicians may ignore advice to cut the dose. Or if a person keeps HIV in control with consistently low drug levels, why tinker?

Khoo discovered his own name among those who declined to heed dose-tweaking advice.

Khoo concluded that TDM plus adherence advice yields no significant virologic or safety benefit. But the study lacked statistical power to exclude such a benefit. Whereas most TDM studies involve PI-treated people, most POPIN participants took an NNRTI, and that drove the results. And because many people already had well-controlled viremia, they had only a modest chance of benefiting from TDM.

**Most drug levels outside therapeutic window**

A cross-sectional study of 151 people taking a PI or an NNRTI underlined two ratios for drug-level monitoring—high variation in antiretroviral exposure from person to person, and high rates of subtherapeutic or potentially toxic drug levels [abstract 70, poster 5.11].

José Moltó (Germans Trias i Pujol University Hospital, Badalona, Spain) and colleagues collected samples from 151 adult clinic patients, half of them taking a PI and half an NNRTI. The most frequently prescribed drugs were LPV/RTV in 56, EFV in 45, and NVP in 34.

Clinic workers drew samples from people taking a twice-daily regimen 10 to 13 hours after the last dose and from people taking a once-daily regimen either (1) 21 to 25 hours after the last dose or (2) eight hours after the last dose in people taking their drugs at bedtime. The cohort was 71% male with a mean age of 41.4 years, and 41% had HCV coinfection.

Interindividual variability in PI and NNRTI concentrations approached 50%, with the widest wavering for LPV, NVP, EFV, and SQV ($n=6$). Defining minimum and maximum drug level targets by the HIVPharmacology.com table, Moltó figured that only 53% of NNRTI concentrations and 85% of PI concentrations lay within the therapeutic range. He scored about 30% of NVP and EFV levels toxic. Subtherapeutic concentrations proved most common with EFV (about 30%), APV (about 20%), and LPV, NFV, and ATV (all less than 20%).

Although Moltó did not warn study participants of the drug monitoring before their clinic visits, poor adherence appeared to explain few of the low drug readings. Most people reported missing no doses in the past week (82%) or missing only one dose (14%). Moltó calculated that poor adherence or drug interactions might explain 44% of subtherapeutic drug levels.

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**Table 17. Inter- and intraindividual variation in drug levels**

<table>
<thead>
<tr>
<th>Drug</th>
<th>$n$</th>
<th>Interindividual variation (CV%)</th>
<th>$n$</th>
<th>Intraindividual variation (CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>51</td>
<td>77.5</td>
<td>13</td>
<td>25.7</td>
</tr>
<tr>
<td>NVP</td>
<td>31</td>
<td>74.5</td>
<td>11</td>
<td>24.9</td>
</tr>
<tr>
<td>LPV</td>
<td>13</td>
<td>73.4</td>
<td>6</td>
<td>48.4</td>
</tr>
</tbody>
</table>

CV = coefficient of variation.
<table>
<thead>
<tr>
<th>First author (abstract no.)</th>
<th>Drug(s) studied</th>
<th>Type of study</th>
<th>n</th>
<th>Main finding</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleosides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colucci (abs 51, poster 4.5)</td>
<td>Elvucitabine (ELV) (5 or 10 mg QD or 15 mg q48h) + LPV/RTV (400/100 mg BID)</td>
<td>Open-label, dose-escalation trial in adults with HIV</td>
<td>24</td>
<td>Plasma ELV levels similar to those without LPV/RTV in HIV-uninfected people</td>
<td>Mean 1.9-log drop in viral load on day 21 with ELV + LPV/RTV</td>
</tr>
<tr>
<td>Kruse (abs 43, poster 3.9)</td>
<td>ddi, d4T, 3TC, CBV, TDF, FTC</td>
<td>Intracellular di- or triphosphate assessments in children</td>
<td>16 (53 PBMC samples)</td>
<td>No major difference between children and adults in PBMC di- or triphosphates</td>
<td>Method used allows TDM of all NRTI triphosphates except AZT-TP</td>
</tr>
<tr>
<td><strong>Nonnucleosides</strong></td>
<td></td>
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<tr>
<td>Timpone (abs 33, poster 2.26)</td>
<td>EFV (600 mg QD) + IDV/RTV (400/400 mg BID) + NRTIs</td>
<td>Open-label, nonrandomized, steady-state trial in ART-experienced adults</td>
<td>8</td>
<td>IDV and RTV levels generally within range of data published earlier</td>
<td>IDV levels generally within range of data published earlier</td>
</tr>
<tr>
<td>Kruse (abs 28, poster 2.21)</td>
<td>EFV (600 or 800 mg QD) + weight-adjusted rifampin</td>
<td>Retrospective study of TDM data on adults taking EFV with rifampin</td>
<td>16</td>
<td>Rifampin did not cause low EFV exposure at the 600-mg EFV dose</td>
<td>High proportion of EFV levels judged toxic with both doses + rifampin</td>
</tr>
<tr>
<td>Hoetelmans (abs 18, poster 2.11)</td>
<td>TMC278 (150 mg QD) + TDF (300 mg QD)</td>
<td>Open-label, randomized crossover in healthy men</td>
<td>16</td>
<td>TDF did not affect PK profile of TMC278; TDF exposure 24% higher with TMC278; judged not clinically relevant</td>
<td>No dosage adjustment needed with TMC278 + TDF</td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
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<tr>
<td>Shelton (abs 24, poster 2.17)</td>
<td>Esomeprazole (20 mg QD) + FPV (1,400 mg BID) or FPV/RTV (700/100 mg BID)</td>
<td>Randomized, open-label, 2-arm, 3-period crossover study in healthy adults</td>
<td>56</td>
<td>No adjustment needed with either dose of FPV</td>
<td>Esomeprazole is a proton pump inhibitor metabolized primarily by CYP2C19 and less by CYP3A4</td>
</tr>
<tr>
<td>Sekar (abs 17, poster 2.10)</td>
<td>Omeprazole (20 mg QD) + TMC114/RTV (400/100 mg BID)</td>
<td>Open-label, randomized, 3-way crossover in healthy adults</td>
<td>17</td>
<td>TMC114/RTV exposure not affected by omeprazole or rifampin</td>
<td>No dose adjustments needed; omeprazole or rifampin not expected to influence antiviral effect of TMC114/RTV</td>
</tr>
<tr>
<td>Sheehan (abs 27, poster 2.20)</td>
<td>Beta carotene (25,000 mg BID) + NFV (1,250 mg BID)</td>
<td>Steady-state PK study in HIV-infected adults</td>
<td>9</td>
<td>Beta carotene did not alter steady-state PKs of NFV or its M8 metabolite</td>
<td>Beta carotene inhibits CYP2C9, CYP2C19, and CYP3A4; combination with NFV appears safe</td>
</tr>
<tr>
<td>van der Lee (abs 25, poster 2.18)</td>
<td>Rosuvastatin + LPV/RTV</td>
<td>Steady-state PK study in HIV-infected adults</td>
<td>14</td>
<td>Rosuvastatin does not significantly affect LPV levels</td>
<td>Rosuvastatin levels not yet measured</td>
</tr>
<tr>
<td>Sabo (abs 42, poster 3.8)</td>
<td>TPV/RTV (500/200 mg) single-dose capsule or oral solution + high-fat breakfast or fasted</td>
<td>Open-label, randomized, single-dose, 3-way crossover in healthy adults</td>
<td>30</td>
<td>Bioavailability of TPV capsules or oral solution optimal with food</td>
<td>TPV oral solution exposure equivalent to capsule exposure</td>
</tr>
<tr>
<td>Cooper (abs 45, poster 3.11)</td>
<td>TPV/RTV (500/200 mg BID) with mild or moderate liver dysfunction*</td>
<td>Open-label case-control study of HIV-uninfected adults with mild or moderate* hepatic disease</td>
<td>9 mild and 3 moderate liver disease and 12 healthy controls</td>
<td>TPV exposure comparable in mild cases and controls; TPV exposure nonsignificantly higher in moderate cases vs controls</td>
<td>TPV/RTV (500/200 mg BID) safe in people with mild liver disease; further study required with moderate liver disease</td>
</tr>
<tr>
<td><strong>CCR5 antagonists</strong></td>
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<tr>
<td>Muirhead (abs 30, poster 2.23)</td>
<td>Combivir (AZT/3TC, 300 mg BID) + maraviroc (300 mg BID) or placebo</td>
<td>Double-blind, randomized, placebo-controlled, 2-way crossover in healthy adults</td>
<td>12</td>
<td>Maraviroc (UK-427 857) had no clinically relevant effect on plasma or urine levels of Combivir</td>
<td>One person stopped maraviroc + Combivir with flu syndrome</td>
</tr>
<tr>
<td>Davis (abs 39, poster 3.5)</td>
<td>Maraviroc (100-300, or 900-ng single dose)</td>
<td>Randomized, single-dose, placebo- and active (moxifloxacin)-controlled 5-way crossover in healthy adults</td>
<td>177</td>
<td>Up to 900 mg of single-dose maraviroc had no effect on QTc interval</td>
<td>With maraviroc, no QTc interval ≥450 ms in men or ≥470 ms in women</td>
</tr>
<tr>
<td>Muirhead (abs 41, poster 3.7)</td>
<td>Maraviroc (300 mg single dose) in Asians and Caucasians</td>
<td>Single-dose study in fasted healthy adults</td>
<td>12 Asian and 12 Caucasian</td>
<td>No between-race difference in exposure after single-dose maraviroc</td>
<td>No clinically relevant changes in ECG data</td>
</tr>
</tbody>
</table>

*Mild = Child-Pugh score ≤5; moderate = Child-Pugh score 7 to 9 < 5 years.

ART = antiretroviral therapy; BID = twice daily; CBV = carbovir, the active triphosphate of ABC; Cmax = maximum concentration; ddi = didanosine; ECG = electrocardiogram; EFV = efavirenz; ELV = elvucitabine; FXV = fosamprenavir; FTC = emtricitabine; IDV = indinavir; LPV = lopinavir; NFV = nelfinavir; NRTI = nucleoside or nucleotide reverse transcriptase inhibitor; PBC = peripheral blood mononuclear cell; PK = pharmacokinetic; QD = once daily; RTV = ritonavir; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; TPV = tipranavir.
Mark Mascolini writes about HIV infection (markmascolini@earthlink.net).

**References**


KEEPING AN EYE ON THE FUTURE OF HIV DISEASE MANAGEMENT

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Addiction

The relationship between non-injection drug use behaviors on progression to AIDS and death in a cohort of HIV-seropositive women in the era of highly active antiretroviral therapy use


AIMS: To evaluate the effects of longitudinal patterns and types of non-injection drug use (NIDU) on HIV progression in the highly active antiretroviral therapy (HAART) era. DESIGN: Women's Intergency AIDS Study (WIHS), a prospective cohort study conducted at six US sites. METHODS: Data were collected semi-annually from 1994 to 2002 on 1,046 HIV-positive women. Multivariate Cox proportional hazards modeling was used to estimate relative hazards for developing AIDS and for death by pattern and type of NIDU. FINDINGS: During follow-up, 285 AIDS events and 287 deaths, of which 177 were AIDS-related, were reported. At baseline, consistent and former NIDU was associated with CD4 counts of <200 cells/microL (43% and 46%, respectively) and viral load >40,000 copies/mL (53% and 55%, respectively). [Participants reporting] c-consistent NIDU reported less HAART use (53%) compared with other NIDU patterns. Stimulant use was associated with CD4 cell counts of <200 cells/microL (53%) and lower HAART initiation (63%) compared with other NIDU types. In multivariate analyses, progression to AIDS was significantly higher among consistent (relative hazard [RH] = 2.52), inconsistent (RH = 1.63) and former (RH = 1.56) users compared with never users; and for stimulant (RH = 2.04) and polydrug (RH = 1.65) users compared with non-users. Progression to all-cause death was higher only among former users (RH = 1.48) compared with never users in multivariate analysis. Non-injection drug use behaviors were not associated with progression to AIDS-related death. CONCLUSIONS: In this study, pattern and type of NIDU were associated with HIV progression to AIDS and all-cause mortality. These differences were associated with lower HAART utilization among [patients reporting] consistent NIDU and use of stimulants, and poor baseline immunological and virological status among former users.

Sexually Transmitted Infections

Increasing detection of asymptomatic syphilis in HIV patients


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

Clinical Infectious Diseases

Accuracy, precision, and consistency of expert HIV type 1 genotype interpretation: an international comparison (The GUESS Study)


BACKGROUND: Resistance testing is considered standard of care in HIV medicine, but there is no standard interpretation system for genotype tests. We sought to determine how much agreement exists within a group of experts in the interpretation of complex genotypes. METHODS: Genotypes from clinical specimens were sent to an international panel of 12 resistance experts. Phenotypic susceptibility testing of these clinical isolates was performed with antivirogram. Experts predicted phenotype fold change category (<2.5-fold change, 2.5-4.0-fold change, >4.0- to 7.0-fold change, >7.0- to 10-fold change, >10- to 20-fold change, >20-fold change) and predicted expected drug activity for each of 16 antiretroviral drugs. Experts were also asked to make treatment recommendations on the basis of the genotype. RESULTS: The experts predicted the exact phenotype fold change category correctly 44% of the time, but they varied widely by antiretroviral drug (range, 25% to 74%). The highest accuracy was observed for lamivudine (74%) and the nonnucleoside reverse transcriptase inhibitors (66% to 69%). Experts generally predicted higher levels of resistance to the remaining nucleoside reverse transcriptase inhibitors than what was found by phenotypic testing. Agreement among experts in predicting phenotype fold change category ranged widely depending on the drug (median agreement, 42% [range, 28% to 74%]); the same pattern was observed in predicting expected drug activity (median agreement, 45% [range, 32% to 87%]). Experts agreed on treatment recommendations in a median of 79% of instances, and recommendations were consistent over time, with blinded restesting. CONCLUSIONS: Although their ability to predict phenotype from a genotype varied for individual antiretroviral drugs, this expert panel had a high degree of agreement in deriving treatment recommendations from the genotype.

ABSTRACTS

Clinics

Effect of antiretroviral drugs on maternal CD4 lymphocyte counts, HIV-1 RNA levels, and anthropometric parameters of their neonates


PURPOSE: To study the effect of antiretroviral drugs administered during pregnancy on CD4 lymphocyte counts and HIV-1 RNA levels of pregnant women and on the anthropometric parameters of their neonates. METHODS: A prospective study was conducted on 57 pregnant women and their neonates divided into three groups: ZDV group, HIV-infected mothers taking zidovudine (n = 20); triple therapy (TT) group, mothers taking zidovudine + lamivudine + nelfinavir (n = 25), and control group, normal women (n = 12). CD4 lymphocyte counts and HIV-1 RNA levels of pregnant women were analyzed during two periods of pregnancy. The perinatal transition took into account preterm rates, birth weight, intrauterine growth restriction, perinatal death, and vertical transmission of HIV-1. Data were analyzed statistically using the nonparametric chi-square, Mann-Whitney, Friedman, Kruskal-Wallis, and Wilcoxon matched pairs tests, with the level of significance set at P < 0.05.

RESULTS: The major maternal demographic and anthropometric data were homogeneous for the various groups. HIV-1 viral burden, which was initially elevated, median of 14,570 copies/mL, was significantly reduced in the TT group, reaching 40 copies/mL. With respect to CD4 lymphocyte counts, there was a significant recovery in the TT group at the end of pregnancy, this value being significantly different from that for the ZDV group (P = 0.0052). There was no difference between groups regarding gestation length, Apgar scores, or neonatal anthropometric classification. There was no case of vertical HIV-1 transmission.

CONCLUSIONS: The results obtained for the present series demonstrate the efficiency and suggest safety of the use of antiretroviral drugs during pregnancy as revealed by anthropometric parameters of the neonate.


Sexually Transmitted Infections

Increasing detection of asymptomatic syphilis in HIV patients


BACKGROUND/OBJECTIVES: The burden of new syphilis diagnoses in London has mainly been in men who have sex with men (MSM), many of whom are coinfected with HIV. Our HIV unit introduced regular serological screening for syphilis during routine follow-up care to detect patients who may be at risk of asymptomatic infection. We assessed if this remained an effective and necessary strategy in the second year since introduction. METHODS: All HIV outpatients with newly positive syphilis serology between May 1, 2002, and April 30, 2003, were identified using a prospectively collected database. Only patients who were asymptomatic at the time of screening were included (cohort B). They were compared to patients in the exact preceding year (cohort A). RESULTS: 2,655 patients had at least one CD4 count measured in the period (surrogate marker for patients having routine follow-up bloods), of whom 2,389 (90%) had syphilis serology performed. Forty individuals were found to have early asymptomatic infection (two were re-infections), compared to 26 patients in cohort A. These 40 patients represented 36% of all patients with infectious syphilis treated within our department and 56% of those who were HIV positive. The event rate in cohort B was 7.3 per 1,000 patient years (confidence interval [CI] 5.2 to 9.9) compared to 2.8 (CI 1.8 to 4.0) in cohort A. CONCLUSION: Routine screening is effective and has detected increasing numbers of HIV outpatients with early asymptomatic syphilis. Our department will continue this strategy for all HIV patients during their follow-up care. We recommend that other units adopt similar initiatives that assist with regional control of the UK syphilis epidemic.
Hepatic steatosis and insulin resistance (IR) are being increasingly recognized as relevant factors in the outcome and management of chronic hepatitis C virus (HCV). Several posters presented at the Digestive Disease Week (DDW), held May 14-19, 2005, in Chicago, addressed these issues.

Liver steatosis has been reported in about 30% to 70% of individuals with chronic HCV infection. One poster at DDW presented the results of a study challenging this association, after finding a lower prevalence of steatosis in HCV-infected patients compared to the general population.1

Data from 215 liver biopsies taken from patients either with liver disease or who were liver donors were examined. The authors found some degree of liver steatosis in 22% (14% mild and 8% moderate to severe) of HCV-infected subjects, compared to 37% (28% mild and 9% moderate to severe) of healthy individuals (P = 0.03), and 6% to 10% of patients with other liver diseases (P = 0.04).

However, in this study the prevalence of steatosis in HCV-infected and healthy subjects is lower and higher, respectively, than previously reported. In addition, although the authors stated that risk factors for steatosis were statistically comparable between both groups, lipid profiles were more unfavorable among liver donors, and they should be included in a multivariate analysis along with other variables such as alcohol use.

Race seems to be a factor affecting the development of hepatic steatosis, according to a study involving 73 HIV/HCV-coinfected patients.2 Grade 2 to 3 steatosis was seen in 34% of Caucasians, 28% of Hispanics, and 4% of African Americans (P = 0.01). According to these findings, Caucasians have the highest risk for the development of liver steatosis among HIV/HCV-coinfected patients.

Likewise, HCV coinfection appears to be a cofactor for the development of steatosis in patients with chronic hepatitis C. In a study examining liver biopsies from 707 subjects, 154 with HIV/HCV coinfection and 554 with HCV alone, steatosis was more frequent and more severe in patients coinfected with HIV (P < 0.001).3

Moreover, microsteatosis, the pattern associated with more mitochondrial damage, was more frequent in the HIV/HCV-coinfection setting (P < 0.001). Interestingly, steatosis was associated with more pronounced immune suppression (P < 0.009), but not with the use of highly active antiretroviral therapy (HAART) (P = 0.3). Further studies are needed to evaluate if HIV itself, immune suppression, or other concurrent factors are involved in the pathogenesis of liver steatosis in HIV/HCV-coinfected subjects.

In the aforementioned study, higher liver fibrosis scores were found to be associated with the presence of steatosis (P < 0.001).3 In like manner, the presence of steatosis was identified by other authors as an independent risk factor for HCV fibrosis in 208 HCV-monoinfected patients (P = 0.0003).4 In another study, also performed with HCV-monoinfected subjects, an association between steatosis and higher fibrosis progression rates was found.5

In the pathogenesis of liver steatosis linked to HCV infection, IR seems to be a key factor. In another study, 400 HCV-1-infected subjects, 134 of them with liver steatosis and 51 individuals with histologically proven non-alcoholic fatty liver disease (NAFLD), were evaluated.6

The assessment of IR was based on the homeostasis model assessment (HOMA) index value. Lower HOMA values were found among subjects with NAFLD, compared to both steatotic (P < 0.001) and non-steatotic (P < 0.05) HCV-infected patients at lower body mass indexes (BMI < 30 kg/m2).

Thus, compared to NAFLD, HCV infection results in a greater degree of IR at lower BMIs. Significant IR was present even in non-steatotic HCV patients, suggesting a direct effect of viral infection on insulin sensitivity, and that IR may precede hepatic steatosis.

In another study, the role of HCV as a risk factor for diabetes mellitus was evaluated in a large database of 480,306 US veterans.7 Hepatitis C infection was found to predict diabetes (odds ratio [OR] 1.48, 95% confidence interval [CI] 1.41-1.54; P < 0.0001), independently of other identified covariates such as age and BMI.

Insulin resistance may have an impact on the response to interferon (IFN)-based therapy of patients with chronic HCV. Another poster reported a secondary analysis of 163 subjects with chronic HCV who had completed a course of IFN-a-2b plus ribavirin, assessing the influence of diabetes on the sustained virological response (SVR).8 Only five of 40 diabetic subjects achieved SVR (12%) compared to 66 of 123 (53%) non-diabetics (P = 0.005). Although very interesting, these data should be confirmed after adjusting for confounding factors.

Further research is needed to better understand the pathogenesis of steatosis and IR in patients monoinfected with HCV or coinfected with HCV/HIV, as well as the clinical implications for the course of the liver disease. We may also need to address these metabolic disturbances in the management of HCV infection.

Reference
“Pavlovian dissent” or honesty?

Continued from page 186

such as United Nations Special Envoy for AIDS in Africa, Stephen Lewis, as a “Pavlovian voice of dissent.” In a speech delivered July 27, 2005, at the 3rd IAS Conference on HIV Pathogenesis and Treatment in Rio de Janeiro, he described “3 by 5” as “brilliant,” declared “it has made all the difference in the world,” and referred to those who choose not to speak in platitudes about the effort as “detractors.” Additionally, Lewis consistently speaks of “3 by 5” as an exclusively WHO effort, though it is in fact the result of efforts advanced by multiple parties, pre- and post-launch of “3 by 5,” including WHO and its regional offices, most notably PAHO and its “Building Blocks” ART scale-up blueprint, which was published in 2000.

To be sure, I have great respect for Lewis and the work he is advancing by giving voice to the more than 25 million Africans living with, and the many more affected by, HIV/AIDS. My respect runs so deep that in 2002 I nominated him for IAPAC’s Jonathan Mann Health-Human Rights Award, which he accepted at the 2003 Honoring Our Heroes tribute dinner held that year in Chicago. While I have no less respect for him personally, I have begun to take umbrage at the shrill nature of his commentary regarding any criticism, however constructive, and at the notion that the WHO should be above reproach.

The flaw is not with the ideal undergirding “3 by 5.” Indeed, contrary to Lewis’ assertion that “the [initiative] launched us on such a trajectory that nothing short of treatment for everyone who needs it is seen as acceptable,” ART scale-up in the developing world had been endorsed, however hesitantly, as far back as 1997 and was gradually and inevitably universally endorsed over several years of hard work by many of the “3 by 5” partners. Rather, the flaw is with the initiative’s execution and a general inability to fully embrace the efforts of its partners pre-launch and support ongoing efforts post-launch.

If partners are not now allowed to offer their expertise in the form of suggestions for improvement or warnings of potential challenges, “3 by 5” will be weaker and less efficient. It will not be in a position to take advantage of the vast knowledge and experience accumulated by the many who have struggled against HIV for so many years. As important, if partners find themselves unsupported by the WHO and competing with it for scarce financial resources, we will be unable to continue to advance activities that strengthen human capacity to deliver ART. If this happens, we all lose.

For example, at a 2003 consultation convened in Geneva around training and accreditation of health care providers to deliver ART, representatives from FPD, IAPAC, and PharmAccess—all of which have been expertly conducting training initiatives worldwide in support of ART scale-up for many years (IAPAC as far back as 2000)—requested that the WHO support efforts to secure additional resources through which training programs could be scaled-up. The WHO’s verbal response was that it is not in its mandate to secure funds for our partners. The actual message, however, was that the WHO produced its own set of “training modules” under the umbrella of its Integrated Management of Adolescent and Adult Illness (IMAI) program, funded through a WHO member state, even though training modules have been in existence since before “3 by 5” was launched in 2002 and re-launched in 2003.

For example, FPD and its partner, the Southern African HIV Clinicians Society (SAHIVS), conduct trainings throughout Southern Africa using a comprehensive trainings module; IAPAC and various partners, including SAHIVS, deliver trainings through a 13-module GALEN course; and PharmAccess utilizes a Web-based curriculum to deliver its nine-module course. A true partner would have avoided duplicating efforts by taking advantage of the expertise offered by such formidable non-profit institutions with sterling reputations for delivering training. Not so…

In a speech also delivered at the 3rd IAS Conference on HIV Pathogenesis and Treatment, Jim Yong Kim, Director of the WHO’s Department of HIV/AIDS, struck a more conciliatory note and expressed a more realistic goal of 2010 as a target year, stating that “now we’ve got to get serious about reaching this target of universal access,” and acknowledging that doing so is “going to be one of the most difficult things that we’ve ever done in the history of public health.” Only together can those of us serious about expanding access to the life-saving benefit of ART achieve this collective goal by 2010 and thus ensure that 3 million people, if not many millions more, remain alive and healthy members of our global society.

Without a doubt, IAPAC remains a committed “3 by 5” partner and stands shoulder-to-shoulder with our WHO colleagues to advance the ideal of universal access to ART. I believe that our efforts to train more than 16,000 physicians and allied health professionals worldwide, as well as providing our GALEN modules free of charge to like-minded partner institutions advancing capacity-building activities in resource-limited countries, is contributing to ART scale-up. Having said that, the WHO owes itself, its partners, and the world an honest discussion about how best to move forward together.

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July 2005

IAPAC Monthly 217
For more than three years the *IAPAC Monthly* has featured members of the International Association of Physicians in AIDS Care (IAPAC), who are asked to bare their souls by answering a series of questions similar in nature to those asked in the famous *Proust Questionnaire*.

This month, *IAPAC Monthly* is proud to feature Renslow Sherer, Director of HIV/STI/TB at Project Hope, and Clinical Associate in the Section of Infectious Diseases at the University of Chicago Hospitals in Chicago.

**Renslow Sherer**

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

“No matter how high or great the throne, what sits on it is the same as your own.”

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

No, my talents are right out there for all to see. It’s my many faults and foibles that I try to keep hidden, mostly unsuccessfully. I love music of all kinds: playing, singing, listening, and dancing to it. I think music is a huge part of life, and always has been very important to me and my family. It’s also one of America’s greatest strengths, and most valuable exports.

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

In my home, with Deb and my extended family.

Who are your mentors or real-life heroes?

Jonathan Mann, for all of the energy and inspiration he gave me over the years; Quentin Young, Bobby Cohen, Jack Raba, and Pat Logan, who taught me how to be a county hospital doctor; Ron Sable, Gordy Schiff, and Mardge Cohen, the most principled people I have ever known. They have led their lives without ever losing sight of their values.

With what historical figure do you most identify?

My dad.

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

Authors: Larry McMurtry, John le Carre, Pablo Neruda, and Arundhati Roy. Composers and musicians: Louis Armstrong, J.S. Bach, the Beach Boys, Beethoven, the Blind Boys of Alabama, David Byrne, Patsy Cline, John Coltrane, Miles Davis, Bob Dylan, Ben Folds, Peter Gabriel, Billie Holiday, Ladysmith Black Mambazo, Mozart, Geoffrey Oryema, Bonnie Raitt, Carlos Santana, Ravi Shankar, and Gillian Welch.

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

Right now.

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

A musician, or maybe a cook.

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

Achievements: Elimination of smallpox. And on a smaller scale, the reversal of the Chicago River—a great public health achievement in alleviating typhoid fever. Failures: Negligence toward the HIV epidemic and preventable childhood illnesses by the developed world. And the failure of men to rise above our dark sides.

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

I’d like to think that the growing idea that loss of life in the developing world to preventable and treatable conditions is unacceptable will continue to grow and spread. This will continue to encourage not only an effort to provide antiretroviral medications, but also to fight malaria and tuberculosis, preventable childhood diseases, and, finally, poverty and starvation in the world.
HIV is a virus, it’s not a moral condition.
Anglican vicar Father Jape Heath, in a June 22, 2005, Reuters report describing a meeting sponsored by the African Network for Religious Leaders Living with and Personally Affected by HIV/AIDS (ANERELA). Heath discovered he was HIV-positive in May 2000, but did not disclose this information to his congregation until 2002. African religious leaders have been criticized for encouraging stigmatization of people infected with HIV. “What we’re encouraging people to do is to know their HIV status and to know there’s no concept of sin attached to HIV,” explained Heath.

I only wish we could get the same focus on the problem of white MSM and crystal meth.
Kevin Garrity, Executive Director of the South Beach AIDS Project, in a June 18, 2005, Miami Herald report about declining rates of new HIV diagnoses among African Americans in Florida. Since 1999, new diagnoses of HIV among African-American men have dropped by 24%, and by 36% in African-American women. Aggressive and rapid testing programs carried out “in medical facilities, in jails, in mobile vans, at pharmacies, with teams of public health officials and community-based organizations” are largely responsible for the decreases, according to Thomas Liberti, Chief of the HIV/AIDS Bureau in the Florida Department of Health. At the same time, Florida has had an increase in new HIV diagnoses among white men who have sex with men (MSM).

We will not be able to get the HIV epidemic under control in this population without learning how to address meth use in this community.
Grant Colfax of the San Francisco Department of Public Health, in a June 16, 2005, article in the Atlanta Journal-Constitution about the HIV epidemic in the United States. Two factors discussed in the article were men who hide their sexual relationships with other men from their female partners, and the escalating problem of crystal methamphetamine use, especially among gay white men. Colfax noted that gay men are three times more likely to use crystal methamphetamine than the general population, and 10 times more likely to report frequent use.

We’re actually right now trying to get in touch with health care advocates in the state to find out if there’s a plan to challenge this particular policy.
Christine Lubinski, Executive Director of the HIV Medicine Association (HIVMA), discussing changes to the State of Mississippi’s Medicaid program in a June 14, 2005, Associated Press report. The changes would limit state Medicaid recipients to five prescriptions per month: two brand-name and three generic drugs. Since most HIV patients are receiving highly active antiretroviral therapy (HAART), which requires a minimum of three drugs, most of which are not available in generic form, there is widespread concern that this policy will force the most economically vulnerable populations in the state into substandard therapy. The changes were scheduled to take effect July 1, 2005.

It’s going to give rise to multi-drug resistant strains.
Robert Gallo, Head of the Institute of Human Virology at the University of Maryland Biotechnology Institute, in a June 24, 2005, report in the Mail & Guardian on the US-Africa Business Summit, hosted by the Corporate Council on Africa. Gallo said that simply sending antiretroviral drugs to Africa will not stem the tide of the epidemic. He emphasized that research on how to appropriately deliver antiretroviral therapy to various populations is essential for avoiding antiretroviral drug resistance.

Asia is at a tipping point in confronting the epidemic.
Jack C. Chow, Assistant Director-General at the World Health Organization, in a June 29, 2005, CNN.com report discussing the AIDS epidemic in Asia. Chow stated that “[i]f the collective response does not match or surpass the pace of the epidemic, we could very well see rates of acceleration matching that of sub-Saharan Africa.” India is second only to South Africa in numbers of HIV infections, and many experts predict that China’s infection rate could climb significantly unless steps are taken to prevent the spread of the epidemic. Vietnam and Indonesia may be facing widespread epidemics as well if steps to curb the infection are not taken quickly. Education, improved health care, and fighting stigma and discrimination against HIV-positive patients were cited as necessary factors in the campaign against HIV/AIDS in Asia.
WHY DOES DESTINY’S CHILD WEAR THE BRACELET?

Michelle, Beyoncé and Kelly wear 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.