January 2004 VOL. 10, NO. 1

IAPAC MONTHLY

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Simpler starters, simpler salvage: Retuning antiretroviral tactics

Mark Mascolini

At the 9th European AIDS Conference, the question of the hour was the cost of simplifying first-line therapy with abacavir-based combinations—a strategy that failed in recent studies. Abacavir-based maintenance after four-drug induction looked like a safer bet. Meanwhile, other work pursued simplification at another point in the treatment history: salvage.

DEPARTMENTS

IAPAC Monthly (ISSN 1545-1089) is published monthly by the International Association of Physicians in AIDS Care. All material published, including editorials and letters, represents the opinions of the authors and does not necessarily reflect the official policy of the International Association of Physicians in AIDS Care, or the institutions with which the authors are affiliated, unless otherwise noted.

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

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REPORT FROM THE PRESIDENT

IAPAC members called on to volunteer

In its 2003 report on the global AIDS pandemic, the Joint United Nations Programme on HIV/AIDS (UNAIDS) told us that HIV/AIDS killed 3 million people in 2003 and infected 5 million more. That the world has not done more to stop this scourge is truly, in the words of UN Special Envoy for HIV/AIDS in Africa Stephen Lewis, "mass murder by complacency,"—failure to act decisively and relentlessly in the face of terrible tragedy.

As I discussed on this page last month, however, at long last there is reason to hope that we can collectively forge ahead with meaningful interventions aimed at saving and improving the lives of countless men, women, and children living with and affected by HIV/AIDS in the developing world. Global political support for the fight against HIV/AIDS is growing, and resources are fast becoming available. Yet, for the goal of expanding access to HIV care and treatment, including antiretroviral therapy, not to remain a hopeless dream, we must harness the strength in our numbers and take action.

As members of the International Association of Physicians in AIDS Care (IAPAC), an association of women and men who are committed to improving treatment options for all people living with HIV disease, we have an opportunity and a duty to meet the tremendous challenges that lie ahead. And so, with all due respect for the realities of our demanding careers, I say to you at this juncture in our global struggle: *Every IAPAC member must do more to wage a concerted effort against the most complex public health challenge of our time.*

We must work with politicians and others in positions of power to help them understand the difficult realities of this pandemic and, subsequently, to craft strategies to address it correctly. There are no more effective activists than those who can speak from a position of expertise, and, by the same token, medical and public health expertise is a privilege bestowed with the proviso that we must marshal it to help others. There is no other choice when the alternative is needless suffering and hastened death.

The expansion of access to antiretroviral therapy on the scale that we envision means that IAPAC members, as healthcare professionals treating people with HIV/AIDS, must do their part to spread HIV clinical treatment knowledge to areas of the world where it is so desperately needed. Physicians and allied healthcare professionals with experience in managing patients on antiretroviral therapy are needed to train their colleagues in areas of the world where antiretroviral therapy has not previously been available. As important, there is a golden opportunity for healthcare professionals in the developed world to serve as in-country mentors to the legions of their developing world colleagues who could use a helping hand in rolling out intricate clinical protocols and strengthening social support networks.

Apropos of that fact, I am pleased to report that IAPAC is taking on new roles and responsibilities that will allow our members to volunteer their time for peer training and mentoring initiatives.

IAPAC has forged partnerships with several key institutions through which our Global AIDS Learning & Evaluation Network (GALEN) may be utilized for healthcare professional capacity building in various countries targeted for funding through the "President's [George W. Bush] Emergency Plan for AIDS Relief," otherwise known as PEPFAR. Among such partnerships are the American International Health Alliance (AIHA) in its bid for a "twinning" center to facilitate capacity building around prevention of mother-to-child transmission (PMTCT) of HIV; Management Sciences for Health (MSH) in its bid to expand access to antiretroviral therapy in Haiti, South Africa, and Uganda; and an IAPAC-led consortium bid to expand access to a continuum of HIV care, including antiretroviral therapy, in Ethiopia, South Africa, and Tanzania.

Suffice it to say that this new direction reflects an ambitious move toward action on a massive scale, and it will be a truly association-wide undertaking. For our efforts to succeed, IAPAC members will need to contribute at every step along the way. Success depends on your willingness to step up to the challenge and give of yourself.

In order to facilitate the volunteer process, the association is expanding, retooling, and renaming our four-year-old African Medical Exchange Program (AMEP). This issue of *IAPAC Monthly* contains a sign-up form for the IAPAC Care and Training Network (ICTN). Please take a few minutes to consider how you might contribute, complete the form, and send it back to us at your earliest convenience. In doing so, you will be joining a cadre of other IAPAC volunteers—many of whom have been busy advancing GALEN trainings in Africa, Eastern Europe, and Latin America in recent years. IAPAC will only contact you on matters relevant to those about which you have expressed an interest, and, as always, we will not share your contact information with any third party.

I hope that you will consider making a substantial volunteer commitment to IAPAC and, if you are working in the developed world, I hope you will consider doing so abroad. If that is not possible, however, there are always options for

important work to be done close to home.

I have already mentioned the need for IAPAC members to involve themselves in promoting political commitment for the treatment and prevention of HIV/AIDS. Additionally, there is work to be done in helping IAPAC prepare training materials and review public health strategies in issue-specific symposia. There will be opportunities to contribute articles and editorial pieces to our various publications, such as a newsletter we are developing specifically on the delivery of antiretroviral therapy in resource-limited settings.

If you have any questions about how to become involved, please feel free to contact me and/or any member of my staff—our e-mail addresses are available at www.iapac.org. Of note, as busy as my staff is, they too will be volunteering of their time in this coming year. As IAPAC's President/CEO, I am privileged to work with women and men who, from the administrative to the programmatic to the executive level, look on their work as something that is done not merely to collect a paycheck, but out of a profound sense of compassion and duty. They have all decided to commit to volunteer hours at local HIV charities above and beyond their already long workweeks. I hope you take this as evidence that IAPAC's commitment runs the length and breadth of the association.

Throughout our lives, each of us has a voice that is audible only to ourselves. A voice which mythologists label "the call." Indeed, it is a call to the value of our lives. The choice of risk over the known and secure. If we never hear the call, perhaps nothing is lost. But, with respect to the human devastation wrought by HIV/AIDS, we have all heard the call. How can we ignore it? ■

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

IAPAC Care and Training Network

Please fill out and return this form via fax at (312) 795-4938 or postal mail to: IAPAC – ICTN, 33 N. LaSalle, Suite 1700, Chicago, IL 60602

First name *Middle initial* *Suffix (MD, MPH, RN, PhD)*

Last name

Address

City/Town *Postal/mailing zip code*

State/Province *Country*

Telephone *Fax*

Email address *Cell/Mobile*

Please check off your areas of experience and interest from among the following:

Experienced	Interested	
❒	❒	Training in HIV clinical management
❒	❒	Mentoring in HIV clinical management
❒	❒	Trouble-shooting in HIV clinical management
❒	❒	Drafting/editing training materials in HIV clinical management
❒	❒	Reviewing (ie, peer-review) materials in HIV clinical management

I hereby authorize the International Association of Physicians in AIDS Care (IAPAC) to compile and store my information for the purpose of registering me in the IAPAC Care and Training Network (ICTN). I understand that IAPAC will not share my information and contact details with any third party without my prior consent.

Signature Date (MM/DD/YYYY)

PUBLIC POLICY

400 percent ritonavir price hike

Keith Alcorn

Abbott Laboratories is facing mounting criticism from several quarters following its decision to quadruple the price of ritonavir (RTV) in the United States. The company emphasizes that the 400 percent price increase "reflects the value that [RTV] brings to combination therapy," and argues that it is necessary to support investment in new formulations of lopinavir (LPV) and RTV that will not require refrigeration, together with a new protease inhibitor (PI) in pre-clinical development.

Ritonavir is now used almost entirely to boost levels of other PIs. The effect of the price increase will be to make Kaletra (a combination capsule containing LPV and RTV) the cheapest boosted PI on the market. However, the move is hurting Abbott Laboratories' relationships with traditional allies in the medical community. Indeed, several national and international groups—including the US-based HIV Medicine Association (HIVMA) and the International Association of Physicians in AIDS Care (IAPAC)—have communicated with Abbott Laboratories expressing dismay that the price increase has taken place in a difficult financial climate for safety-net programs such as Medicaid and the AIDS Drug Assistance Program (ADAP).

In an open letter to Abbott Laboratories, the HIVMA's Paul Volberding and Dan Kuritzkes (Chairman and Vice Chairman, respectively), wrote: "While we recognize the value of ritonavir, we are alarmed by your decision to raise the cost of protease inhibitor regimens to the point where many people who need these life-saving drug combinations will struggle to pay for them or won't have access to them at all."

IAPAC President/CEO José M. Zuniga, while acknowledging RTV's value as a pharmacokinetic enhancer of other PIs, echoed the HIVMA's concern and added that the upward curve in HIV drug pricing—most recently with enfuvirtide (ENF) and now with RTV—is an unsustainable trend.

"The system charged with delivering care to medically indigent people living with HIV/AIDS in the United States—and, indeed, in most countries where antiretroviral therapy is available—cannot withstand the financial pressure of significant spikes in commodities pricing each time a new drug or new drug formulation is introduced and/or when a company decides it has under-priced its product," Zuniga wrote in a December 10, 2003, communiqué to Abbott Laboratories.

Zuniga explained that numerous IAPAC physician members are upset by Abbott Laboratories' decision above and beyond a matter of principle, especially since they are already dealing with significant budget shortfalls in state safety-net programs that are struggling to keep pace with an increasingly complex and expensive HIV drug armamentarium.

IAPAC member Joseph Eron (University of North Carolina) also shares a widespread concern over the longer-term implications of the price increase among physicians, saying that, "While I understand the business perspective, I am dismayed that this happened. This move has dramatic implications for programs that have limited funding such as Medicaid, and ADAP in some states."

How much?!

Effective December 4, 2003, Abbott Laboratories increased the wholesale price of RTV from US$205.74 to US$1,028.71 for 120 100mg capsules—the equivalent of US$515 a month if RTV is being dosed at 100 mg twice daily with another PI. The previous cost of the drug lay around US$100 to US$110 a month when dosing at 100 mg twice daily. However, the actual cost to the most vulnerable consumers in the United States—those without insurance who must pay directly for their medicines—is unpredictable due to the complex discounts and charging structures that operate between pharmacies.

Abbott Laboratories claims that 90 percent of US patients will not be affected by the price increase because they are covered by medical insurance of some sort, and any patient who cannot afford RTV, or whose insurer refuses to cover the cost of the drug, will be able to receive free medication. The company also promises to drop the onerous means testing requirement, in which patients have to provide detailed proof of income for all family members in order to receive the drug free of charge.

Company representatives also say that RTV's price will remain neutral for public payors, including state Medicaid programs. Drug companies are only allowed to increase the prices they charge public payors by the rate of inflation each year. The cost to state ADAPs has also been frozen at the old price until March 2005, when the entire funding structure for ADAPs is due to be reviewed by the US Congress during the Ryan White CARE Act reauthorization.

However, a price hike is possible after this point for both Medicaid and ADAPs, since Abbott Laboratories has promised new formulations of LPV and RTV by 2005. The company would be free to charge a higher price to these programs for a new formulation of RTV, and might agree in return to offer generous discounts in return for the ability to charge substantially more for RTV than the current Medicaid price.

The HIVMA warns that even though the price for ADAPs has been frozen, pharmacies will bill ADAPs at the new

price, leaving them to collect a rebate from the manufacturer. This will take up to six months, and could leave state ADAPs in a very difficult financial position.

Consequences for competitors

The effect of the RTV price increase is likely to focus attention on the pricing of all new HIV drugs, and will be particularly troubling for the development of TPV, Boehringer Ingelheim's new PI, which must be boosted with a total of 400 mg of RTV daily. Boehringer Ingelheim is widely believed to be contemplating a price for TPV that would lie somewhere close to the cost of the new fusion inhibitor ENF (around US$20,000/year).

The RTV price increase will add approximately US$9,000 to the cost of using TPV, which may force Boehringer Ingelheim either to cut the price of TPV drastically, or limp to market with a product that will cost almost 40 percent more than ENF (a drug which forced many state ADAPs to introduce waiting lists).

The move is also being interpreted as a bid to see off competition in the PI market from Bristol-Myers Squibb's atazanavir (ATV), which costs around US$700 per month. Boosting once daily with 100 mg of RTV added around US$50 to this cost prior to the price increase. Prior to the price increase, ATV/r was slightly more expensive than LPV/r. The effect of the price increase is to push the cost of ATV/r up by at least US$260 per month, making it substantially more expensive than LPV/r.

However, IAPAC Trustee Mike Youle (Royal Free Hospital, London) believes that Abbott Laboratories' action could have an unintended effect on Bristol-Myers Squibb's ATV development strategy. "This makes it much more attractive for BMS to study the use of atazanavir 600 mg as an alternative to Kaletra, since you may achieve very good blood levels at that dose without the need for ritonavir boosting." Bristol-Myers Squibb shelved investigation of a 600 mg ATV dose after phase II studies showed a higher rate of treatment-limiting hyperbilirubinemia at that dose.

The price increase will have an even more inflationary effect on the cost of the recently approved prodrug of amprenavir (APV) marketed by GlaxoSmithKline as Lexiva. A US Food and Drug Administration (FDA) license for this drug was granted with the recommendation that it should be boosted with RTV when used in antiretroviral treatment-experienced patients, at a dose of 700 mg of APV and 100 mg of RTV twice daily. That is an extra US$400-plus per month for any patient who needs APV due to their drug resistance pattern. To dose it once daily would be just as expensive.

How long before Europe faces a similar price hike?

Although Abbott Laboratories has assured physicians and community groups in the United Kingdom that the price increase only applies to the United States, there is mounting anxiety across Europe that the company will seek to price its new formulations, especially RTV, at much higher levels. Publicly funded healthcare budgets in Europe may not have the same resilience as US insurance funds when it comes to a large hike in the price of RTV.

Concern in the United Kingdom focuses on the rising cost of salvage therapy, particularly where ENF and TPV might be used together. Some physicians doubt whether National Health System (NHS) purchasers would consider such treatment cost-effective if its annual cost approached £30,000 a year. Recent research based on the TORO 1 and 2 studies of ENF showed that in advanced HIV patients, the cost per quality-adjusted life year of a regimen containing ENF was £23,200. Forcing the price of other drugs up to the ENF level, they argue, would make salvage therapy for HIV infection unattractive to the NHS in comparison to other competing claims.

What is this all about?

Abbott insists that the price rise is not aimed at fixing its competitors, but at delivering better drugs for patients. Others see a longer range plan to destabilize the PI marketplace by changing the economics of treatment at the very moment promising data are trickling out on the use of single-boosted PIs as maintenance treatment, on dual-boosted PI treatment, and on regimens sparing nucleoside reverse transcriptase inhibitors (NRTIs).

In a December 18, 2003, report, the electronic news service www.aidsmap.com quoted an anonymous pharmaceutical company research scientist as stating that, "this isn't just an attack on competitors' pricing, it's an attack on their research strategies. Why bother investing in these areas if Abbott has effectively priced you out of the market in the [United States]?"

The argument goes that by pricing others out of the market, Abbott Laboratories will effectively shape the evidence base in such a way as to ensure that all roads lead to its products. "It's a scary abuse of monopoly," the anonymous researcher asserted, suggesting that all other research into single-boosted PI and any dual-boosted PI that excludes LPV will grind to a halt.

Is one company to blame?

The dispute plays into a wider debate beginning to take shape in the United States, over the extent to which the pharmaceutical industry should be free to set prices. In the United Kingdom, the pharmaceutical industry has been warned that the days of the blank check may be over, and in many other developed countries, spiraling drug costs are forcing tougher negotiations over price.

A collision between the needs of the pharmaceutical industry (for profit and shareholder value), governments (to stretch tax revenue), and patients (for life-sustaining treatment) is fast approaching in North America and Europe, and there are only two possible solutions:

- A complete overhaul of the profit structure in the pharmaceutical sector, leading at one end of the spectrum to the consolidation of the pharmaceutical sector into a handful of key players, or at the other end to the breakup of big pharma and the advent of a writer/publisher type arrangement, in which biotech companies invent drugs and multiple generic manufacturers compete to license those products, with phase III and IV research funded by health maintenance organizations and public payers who seek to define which drugs represent best value.
- Stricter regulation of price without any structural change in the industry, as proposed recently by *The Economist*, by which governments reward genuine innovation with higher prices but force drug companies to submit to tighter price regulation.

Either way, a more sophisticated conversation about value and pricing between industry, physicians, and patients will be forced to evolve in the next few years. ■

Editor's Note: *Reprinted and adapted with permission from www.aidsmap.com (first e-published December 18, 2003).*

Editor's Note: *The following letter was issued December 23, 2003, by John Leonard, Abbott Laboratories' Vice President for Global Pharmaceutical Development, in response to physicians' queries about the 400 percent increase in the price of its protease inhibitor, ritonavir.*

Dear HIV-treating clinician:

I want to take this opportunity to respond to your inquiry regarding the recent re-pricing of Norvir (ritonavir). We hear and understand your issues and share your ultimate concern — ensuring that patients continue to have access to effective HIV therapies.

Ensuring patient access

We did not make this pricing decision lightly, and when doing so, carefully considered patients' ability to access this drug. We took several key steps to ensure that patients are not adversely impacted. As you may know, patients fall into one of three coverage categories:

1) those without prescription drug coverage who pay out of pocket (approximately 5 percent);
2) those who receive public assistance through AIDS Drug Assistance Programs (ADAPs) or Medicaid (approximately 55 percent); and
3) those who are covered by private medical insurance (approximately 40 percent).

For patients without prescription drug coverage or public assistance, we expanded our Patient Assistance Program (PAP) for Norvir to ensure that all patients without drug coverage can receive this drug for free from Abbott, regardless of their financial status. In fact, our PAP for Norvir is the only program in the industry that does not include a financial means requirement.

Since implementing the new price on December 4, [2003,] we have approved all Norvir PAP applications within 24 hours. If you have patients in need of assistance, they can receive an application by calling (800) 222-6885 (select option 2), or by visiting www.abbottvirology.com.

More than half of all patients with HIV receive their drugs through public assistance programs such as ADAPs or Medicaid. Abbott has ensured that these patients will not be impacted by this re-pricing. Specifically, we met with state ADAP directors over the past three weeks, and have issued a new Memo of Commitment honoring the former Norvir price for all ADAPs through June 2005.

We have also contacted every state Medicaid program to affirm that the cost of Norvir will be held at the former price. We are committed to ongoing collaboration with public assistance programs to ensure patient access in the future.

Patients covered through private insurance should not be adversely impacted either. Within the past week, we have contacted many top private insurance providers, including PacifiCare and HealthNet, to address issues regarding access and co-pays/premiums. None of these providers currently restrict access to HIV medications through a formulary.

In addition, none of these plans intend to increase co-pays or premiums based on this pricing action. It is important to note that less than 10 percent of privately insured patients pay a percentage of the prescription cost versus a flat co-pay. It is expected that these patients are protected and will not pay more annually due to out-of-pocket maximums.

Balancing new programs with economic realities

Ultimately, access to more and better HIV therapies is in the best interest of patients. This new price is necessary to support our ability to continue research to bring a next generation HIV medication to market, to develop improved formulations of our existing products, and to continue our commitment to the developing world. In fact, we are currently investing in new HIV and hepatitis C compounds, as well as new formulations of both of our HIV products. One of Abbott's goals is to develop products that can be stored at room temperature, improving their value and convenience to patients both here and in the developing world.

The changing role of Norvir

Since Norvir was originally launched, the role and value of Norvir in the treatment of patients with HIV/AIDS has changed dramatically. In 1996, Norvir was prescribed as a stand-alone protease inhibitor at a recommended daily dose of 1,200 mg and a daily price of US$20.52.

Today, Norvir is primarily used at low doses of 100 mg to 200 mg in combination with other protease inhibitors, with 100 mg being the most commonly prescribed daily dose. At the new price of US$8.57 per 100 mg, Norvir is most often the lowest cost component of a protease inhibitor-based regimen. For example, when you combine Norvir with a regimen based on newly approved therapies such as Reyataz (atazanavir) at US$22.08 per day, Norvir continues to represent a fraction, typically one-fifth, of the daily cost of therapy. ■

Restoring anti-HBV immunity in HIV/HBV-coinfected patients

Michael Carter

Antiretroviral therapy can partially restore specific immune responses against hepatitis B virus (HBV) in patients coinfected with HIV and HBV, even if their antiretroviral regimen does not include drugs with a specific anti-HBV effect, according to a small study published in the December 15, 2003, *Journal of Infectious Diseases*.

Investigators in London studied five HIV/HBV-coinfected patients for 24 weeks after either starting antiretroviral therapy or adding an antiretroviral drug to the regimen that was also active against HBV. The researchers wished to see whether antiretroviral therapy, with or without an anti-HBV drug, was capable of inducing HBV-specific immune responses. The research was prompted by studies showing that HIV-negative patients infected with HBV were able to recover some HBV-specific CD4 and CD8 immune response after treatment with lamivudine (3TC), which is active against both HIV and HBV.

After 24 weeks of antiretroviral therapy, which did not include any drugs active against HBV, two patients saw a return of HBV-specific CD8 cell response. A third patient, who was initially taking dual nucleoside reverse transcriptase inhibitor (NRTI) therapy, experienced a return of HBV specific CD8 cell response after the addition of the NRTI adefovir (which, although effective against both HIV and HBV, is only licensed for the treatment of HBV because the dose needed for HIV treatment causes toxicities). This patient also had a return of HBV specific CD4 cell response.

The recovery of immune responses to HBV was preceded by a reduction in HBV viral load and levels of HBV surface antigen. A fall in HBV viral load was accompanied by an improvement in ALT levels. CD4 counts increased significantly in three patients in the study, but only one of these experienced a restoration of HBV-specific immune response. Although HIV viral load fell significantly in three patients, this was only accompanied by specific immune responses against HBV in one patient.

"Our preliminary findings from this longitudinal study of five patients need to be confirmed in larger studies," cautioned the investigators. However, they added that, "it appears that [antiretroviral therapy] alone may be insufficient for reconstitution of HBV-specific responses." However, some reconstitution of specific responses can occur with a reduction in HBV viral load, even if a patient has a high HIV viral load. ■

Editor's Note: *Reprinted with permission from www.aidsmap.com (first e-published December 22, 2003).*

TMC 125 possibly effective against NNRTI-resistant HIV

TMC 125, a new non-nucleoside reverse transcriptase inhibitor (NNRTI), reduces viral load in HIV-infected patients with high-level phenotypic NNRTI resistance, European investigators reported in a fast-track article published in the December 5, 2003, issue of *AIDS*. Published in the same issue was a concise communication in which another group of European researchers claimed that monotherapy with TMC 125 in previously untreated patients leads to a rate of decline of plasma HIV RNA no less than that associated with a five-drug regimen during one week of therapy.

TMC 125 is a diarylpyrimidine derivative with molecular flexibility to accommodate mutational changes in the binding pocket of the reverse transcriptase. Brian G. Gazzard *et al* (Chelsea and Westminster Hospital, London) explained that *in vitro* studies of TMC 125 showed activity against more than 1,000 NNRTI-resistant HIV mutants.

In a proof-of-concept study, Gazzard *et al* administered TMC 125 at 900 mg twice daily for seven days to 15 patients previously treated with NNRTI-containing regimens, specifically efavirenz (EFV) or nevirapine (NVP). The median number of NNRTI mutations was two; three patients had three mutations, and one had four. They also had nucleoside reverse transcriptase inhibitor (NRTI) mutations, and all but one had protease mutations.

When TMC 125 was substituted for the previous NNRTI, viral load decay rate was 0.13 $\log_{10}$ HIV RNA copies/mL per day. Median decrease at day 8 was 0.89 $\log_{10}$ copies/mL, and seven patients had a decrease of >1 $\log_{10}$.There were no severe adverse events. Most commonly reported mild or moderate events were diarrhea and headache.

If further studies confirm these findings, the authors suggest that TMC 125 may be of benefit following failure with a current NNRTI, and may even be used in NNRTI-naive patients.

In the concise communication, Joep MA Lange *et al* (University of Amsterdam, The Netherlands) compared treatment efficacy during one week of therapy with TMC 125 or with a five-drug regimen (lamivudine [3TC], abacavir [ABC], indinavir [IDV], NVP, and zidovudine [ZDV] or stavudine [d4T]) in antiretroviral therapy-naive patients.

In the 12 patients on TMC 125, the median plasma HIV RNA decline was 1.92 $\log_{10}$ copies/mL, compared with 1.76 $\log_{10}$ copies/mL in 11 patients on the five-drug regimen. Median increases in CD4 cells were 119 and 60 cells/L in the two groups, respectively.

Lange *et al* suggest that, "starting treatment with a TMC 125-containing regimen could give a better suppression of HIV replication in the long run."

Editor's Note: *This Reuters Health article was first e-published January 9, 2004.*

Simpler starters, simpler salvage: Retuning antiretroviral tactics

Mark Mascolini

How will 2003 be remembered, antiretrovirally speaking? Set aside, for the moment, the most obvious answer to that question: 2003 was the year when AIDS activism won its biggest prize—serious work toward making antiretrovirals as easy to get in Gaborone as in Hollywood, in Port-au-Prince as in Portland.

Bill Clinton's AIDS foundation brokered a deal with four top generic drugmakers to trim price tags even more for national antiretroviral rollouts in 12 Caribbean and four African countries. Attendees at Warsaw's 9th European AIDS Conference (9th EAC) heard of early antiretroviral success at a bucolic outpost in Botswana, whose government earned high marks for its commitment to nationwide treatment. Even foot-dragging South Africa took a big step in the right direction, promising a comprehensive treatment program of its own.

But set aside all that and consider only antiretroviral tactics. Maybe many will recall 2003 as the year that presalvage drug breaks bit the dust. (Two studies in which the strategy failed got published[1,2] and a third, by Christine Katlama's group at Paris's Pitié-Salpêtrière Hospital, confirmed that failure at the 9th EAC [abstracts 7.4/10 and F7/5]). Some might vote for 2003 as the year that brought a fourth antiretroviral class to market, the fusion/entry inhibitors, represented by enfuvirtide (ENF). (Trimeris and Roche tried to salvage lagging sales of the salvage drug by advertising directly to people who may need it.) Or perhaps 2003 will go down as the year when non-nucleosides (NNRTIs) firmly out-elbowed protease inhibitors (PIs) as the fulcrum of first-line therapy.

But if one judges these contests by sheer weight of evidence, many will remember 2003 as the year when triple-nucleoside (NRTI) therapy stumbled as a first-line tactic. Despite the alluring, often once-daily simplicity of these regimens, they came up short—usually disastrously short—in five clinical trials:

- Trizivir (TZV), the twice-daily single-pill version of zidovudine (ZDV), lamivudine (3TC), and abacavir (ABC), did not match TZV/efavirenz (EFV) or Combivir (CBV)/EFV in ACTG protocol 5095.[3] Still, 74 percent in the TZV arm had a 48-week viral load below 200 copies/mL.
- Once-daily 3TC, ABC, and tenofovir disoproxil fumarate (TDF) failed in 49 percent of treatment-naive people in a randomized trial[4] and in 58 percent in a single-arm study.[5]
- ABC plus didanosine (ddI) and stavudine (d4T) came in third in a randomized comparison with ZDV/3TC plus either saquinavir (SQV)/ritonavir (RTV) or nelfinavir (NFV)/nevirapine (NVP).[6]
- Once-a-day ddI, 3TC, and TDF failed to control viral replication in 22 of 24 treatment-naive people.[7]

Glaxo advised clinicians to stay away from 3TC/ABC/TDF, and Gilead steered them clear of ddI/3TC/TDF. At this point few physicians would consider combining ddI and d4T when they have other nucleoside options. But what about TZV? A 48-week 74 percent intent-to-treat success

rate, though significantly inferior to EFV-containing combos,[3] would place TZV ahead of more than a few regimens tested in recent years.

Nevertheless, the British HIV Association (BHIVA) revised its guidelines to discourage up-front therapy with TZV, except in "special situations," such as anticipated poor adherence or cotreatment of another disease, like tuberculosis.[8] US Department of Health and Human Services (DHHS) guidelines, updated in November 2003, called TZV and d4T/3TC/ABC "alternative" first-line regimens that "should ONLY be used when an NNRTI-based or a PI-based regimen cannot or should not be used as initial therapy."[9]

People puzzled about the best role for TZV may have found some answers in Warsaw, where several research teams offered fresh data on the 3-in-1 pill. Their findings support BHIVA guidance to consider TZV a still-worthy alternative for certain people starting their first antiretrovirals, perhaps injecting drug users in particular. Other trials confirmed TZV's place as an easier-to-take maintenance regimen after tight control of HIV with more complex combos—or for people having a hard time sticking with another regimen. And a big chart review showed that TZV, when coupled with TDF, scores points as a salvage regimen, even in a cohort with lots of ZDV, 3TC, and ABC experience.

Yet this recent bolus of nucleoside/nucleotide news makes one thing clear: Quite apart from the risk of toxicity failures, some of these combinations may have an inherent antiviral flaw bequeathed by a high degree of cross-resistance. One Warsaw study confirmed a higher rate of failure with regimens joining ABC and TDF, two parts of the triple-nuke therapy that fell flat in the Glaxo trial[4] and the smaller pilot study.[5]

So suppose you and the person waiting to walk into your office are fed up with nucleosides and tides. You don't want to use three; you don't want to use two; you don't even want to use one. But you're anxious about risking NNRTIs with a boosted PI because a spell of bad adherence will eliminate NVP and EFV for good. How about two boosted PIs? How about one?

Two studies reviewed in Warsaw found merit with the sanctuary-penetrating salvage threesome of indinavir (IDV), lopinavir (LPV), and RTV. One prospective trial reported before Warsaw, and a retrospective analysis at the 9th EAC, showed that some people can get by with LPV/RTV alone, at least for a while. Before one recoils in a Pavlovian fit from this apparent rebirth of monotherapy, one should know that LPV's maker, Abbott, has more than a passing interest in prospects for solo LPV/RTV. Trials are on the drawing board.

Days were short in northern Europe as the winter solstice crept nigh. And at night the mud puddles made umber ice. But when the sun shone and tempered temperatures, the 9th EAC warmed PowerPoint projectors with more than a little antiretroviral news. Between data on triple nukes and solitary PIs, attendees also learned:

- Three drugs work as well as four in first-line treatment of advanced disease.
- Once-daily LPV/RTV holds its own against twice-daily dosing.
- Once-a-day EFV with ddI/TDF or 3TC/ABC handcuffs HIV and makes directly observed therapy (DOT) possible.
- In a US HIV cohort, cardiovascular disease outranked kidney and liver complaints as a ticket to the hospital.
- Craniosynostosis—premature closure of one or more cranial sutures—may be more common in HIV-exposed children.
- One clinic reported an 88 percent nine- to 12-month success rate with early NNRTI regimens. The clinic is in Botswana's outback.

HOW TO USE TRIZIVIR

When TZV failed to keep pace with two EFV-based regimens in ACTG 5095,[3] clinicians who have used the ZDV/3TC/ABC pill successfully hardly seemed ready to abandon it. After principal investigator Roy Gulick (Cornell University) disclosed the ACTG 5095 results at the 2nd IAS Conference on HIV Pathogenesis & Treatment in Paris, Princy Kumar (Georgetown University, Washington, DC) argued that TZV still merits a first-line shot because of its convenience, tolerability, and lower copayments, and because its failure leaves good options for stalwart second- and third-line regimens.

Gulick did not contest those points, and he acknowledged that the trial's definition of failure—two viral loads above 200 copies/mL after treatment week 16—may not be every clinician's definition of failure for everyone starting antiretrovirals. But for people who believe in randomized, double-blind, placebo-controlled trials, he reminded attendees, ACTG 5095 offers acid-test proof that TZV lets more people down than does TZV/EFV or CBV/EFV.

Who *are* the people who may have the best chance with up-front TZV? Two studies unveiled in Warsaw suggested answers, while other trials offered insights into simplifying more complex regimens by switching to TZV. An interesting retrospective study weighed the merits of TZV/TDF at the other end of the treatment history—as salvage.

When is TZV still a first-line option?

Myrto Astriti (Pitié-Salpêtrière Hospital, Paris) asked the question of the hour in her abstract title: "Trizivir in ARV-naive HIV patients: Can it still be considered as a first-line treatment option?" Her answer, based on a retrospective analysis of 120 treatment-naive people who started TZV, was "yes" [abstract F1/2].

Women made up a little more than one third of the cohort; 56 percent were Caucasian and 40 percent African. They began treatment with a median viral load of 4.96 logs (about 91,000 copies/mL) and a median CD4 count of 233 cells/mm^3; 28 percent had AIDS. Both missing-data-equal-failure and on-treatment analyses at 48 weeks buttressed an earlier finding on first-line TZV[10]: People with a pretreatment load below 100,000 copies/mL respond better (Table 1). Although this retrospective study and the published randomized trial[10] both tied virologic response to baseline load, that criterion fails as an absolute predictor of response: In ACTG 5095 time to failure with TZV proved significantly faster than in the other study arm regardless of starting viral load.

Defining virologic failure as two consecutive RNA readings above 200 copies/mL after week 12, Astriti counted only nine (7.5 percent). Five of those nine never ventured into sub-200 territory, while the other four had rebounds between months 6 and 12. Five of the nine people in whom TZV failed admitted shaky adherence. Twenty-two people stopped TZV because of side effects. Although 11 of 22 quit because of apparent hypersensitivity reactions to ABC, clinicians later judged four of

Table 1. **Viral load-based responses to first-line TZV (*n* = 120)**

	Baseline RNA <100,000 copies/mL (%)	*Baseline RNA >100,000 copies/mL (%)*	*P*
<200 copies/mL, week 24, M = F	86	66	<0.04
<200 copies/mL, week 48, M = F	73	59	<0.001
<200 copies/mL, week 24, on treatment	92	82	NS
<200 copies/mL, week 48, on treatment	93	75	<0.04

M = F = missing-equal-failure analysis; NS = not statistically significant.
Source: Myrto Astriti, abstract F1/2.

those reactions "unlikely" or "not probable."

This study and ACTG 5095[3] show that about three quarters of treatment-naive people can expect to control viral replication for a year or more with TZV. Schlomo Staszewski (J.W. Goethe University, Frankfurt), who headed a comparison of TZV with IDV, ZDV, and 3TC,[10] noted after Astriti's talk that 75 percent who started TZV as a first-line regimen in his clinic continue to take the tripartite pill after four years.

TZV's one-pill twice-daily dosing makes it a strong candidate for people with stressed or disorganized lives, such as injecting drug users (IDUs). But do IDUs really do well with TZV? A prospective cohort study by Robert Jablonka (University of Essen, Germany) and colleagues in Frankfurt showed that they do for 48 weeks—as long as they stick with the regimen [abstract 10.1/13].

Jablonka tracked 62 treatment-naive IDUs with an average age of 37 years, a mean CD4 count of 279 cells/mm^3 (range 26 to 852 cells/mm^3), and a mean viral load of 174,223 copies/mL (range 200 to 1,000,000 copies/mL). Twenty-four of them (39 percent) were women, and all were enrolled in opiate maintenance programs.

A high dropout rate underlines the potential difficulties of treating IDUs. Twenty-four people quit the cohort before week 48, and another seven stopped showing up for clinic visits. Jablonka did not report how many dropouts could be tied to side effects, but he noted that the most common toxicities were hematologic in 13, gastrointestinal in seven, and hypersensitivity reactions in five. An opportunistic infection—oral thrush—developed in three people during treatment.

In a week-48 on-treatment analysis, 71 percent had a viral load below 50 copies/mL. In an intent-to-treat analysis including dropouts and people lost to follow-up, the sub-50 rate measured only 34 percent. Among people who completed 48 weeks of treatment, the average viral load fell 2.69 logs and the average CD4 count added 112 cells/mm^3. The high starting viral loads in this cohort probably undercut the chance of success. Jablonka did not report virologic responses according to baseline load.

The TZV switch: Simpler and still strong?

Swapping a suppressive regimen for TZV—or for any nucleoside-containing regimen—can be risky in people who may harbor nucleoside-resistant virus. But people who never endured failure of a nucleoside-based regimen often get good mileage out of TZV, according to results of two small switch studies.

Jacques Reynes (University Hospital Center, Montpelier, France) and colleagues at other French hospitals studied 18 people who maintained a viral load below 50 copies/mL while taking TZV plus NFV for 48 weeks [abstract 7.5/3]. So the small study group consisted entirely of people who tolerated TZV well for nearly a year. One person dropped out of the study when she became pregnant, and two died from causes not related to HIV. Of the remaining 15 people, 14 had a viral load test after taking TZV alone for 48 weeks, and 11 of them (79 percent) still had a viral load under 50 copies/mL. RNA loads in the remaining three measured 85, 152, and 344 copies/mL. The one person who did not have a week-48 viral load test had fewer than 50 copies/mL at week 40.

The median CD4 count rose 99 cells/mm^3 between the switch to TZV alone and week 48, but not everyone gained CD4 cells during that period. The CD4 change ranged from -65 to +194 cells/mm^3. Median fasting cholesterol, triglycerides, and glucose remained stable and within normal ranges during 48 weeks of TZV therapy. Clinicians noted no further signs of lipodystrophy during the 48-week study, and some signs appeared to resolve.

A similar but longer simplification study confirmed control of viremia with TZV alone after a 48-week induction regimen of TZV and, in this trial, EFV [abstract 7.5/12]. Pierre de Truchis (Centres Hospitaliers Ile de France, Garches) reported that 17 of 20 people (85 percent) who dropped EFV and continued TZV maintained a viral load below 50 copies/mL after 96 weeks on the maintenance regimen. Of the three people who did not reach week 96 of TZV-only therapy, one quit because of side effects (arteritis in the legs), one stopped after adhering poorly to the regimen, and one stopped returning for visits. Drug-related insulin-dependent diabetes developed in one person while taking TZV, but that person did not drop out. From the point when these 20 people switched to TZV alone, the median CD4 count rose 56 cells/mm^3, but the range was again wide: -206 to +270 cells/mm^3.

Fasting triglycerides did not change much after the switch to TZV alone. Median cholesterol levels rose 0.67 mmol/L (P = 0.004) during TZV/EFV induction and fell 0.453 mmol/L after 96 weeks of TZV alone. Median glucose rose from 4.58 mmol/L after 48 weeks of TZV/EFV to 5.09 mmol/L after 98 weeks of TZV. Proviral DNA levels, low after 48 weeks of induction therapy, did not rebound during TZV maintenance.

A retrospective study showed that TZV maintenance worked in most people with PI (98 percent) and/or NNRTI (77 percent) experience, but earlier therapy with one or two nucleosides raised the risk of virologic failure 2.75 and 3.35 times respectively [abstract 7.5/20]. Jorge Vergas (San Carlos Hospital Clinic, Madrid) counted eight virologic failures among 74 people (11 percent) over 48 weeks of follow-up, two in people who had tried nucleoside monotherapy and four in people who had taken dual-nuke therapy. Six people dropped out because of virologic failure, five because of hypersensitivity reactions, and three for other reasons. An on-treatment analysis showed that about 85 percent maintained a viral load under 50 copies/mL through 48 weeks:

- Week 12: 57 of 62 (92 percent) <50 copies/mL

- Week 24: 40 of 47 (85 percent) <50 copies/mL
- Week 36: 27 of 32 (84 percent) <50 copies/mL
- Week 48: 17 of 20 (85 percent) <50 copies/mL

Total cholesterol and triglycerides both dropped about 50 mg/dL during 48 weeks of TZV therapy, while CD4 counts usually climbed.

Simpler salvage with TZV/TDF

Although regimens including only nucleosides with or without the nucleotide TDF do not keep pace with PI or NNRTI combos as first-line therapy, a retrospective study at London's Chelsea and Westminster Hospital suggested that TZV plus TDF often serves well in salvage [abstract 7.4/5]. The thinking here, explained Victoria Latham, is that rescue regimens typically become more complex after each new failure. Yet that very complexity imperils their success by making adherence tougher. So what if you make a salvage regimen *simpler* than a failing combination? Twice-daily TZV plus once-daily TDF is pretty simple.

Latham and coworkers checked the records of 122 people who switched to TZV/TDF after at least one regimen flopped virologically. The study group had tried an average of four earlier regimens, 87 percent had used 3TC, 77 percent ZDV, 55 percent ABC, and 26 percent TDF. Only 6 percent had taken none of those drugs.

Six months after changing to TZV/TDF, 31 people (25 percent) were no longer taking the regimen, six (5 percent) because of virologic failure and the others because of side effects or loss to follow-up. Among the 91 people who took TZV/TDF for six months, the average CD4 count jumped 80 cells/mm^3, and 56 (62 percent) reached a viral load below 50 copies/mL. Among 28 people with at least one year of follow-up, the average CD4 count rose 124 cells/mm^3 and 15 (54 percent) had a sub-50 viral load. After treatment month 6, another seven people had a virologic failure.

Using ZDV-induced mean cell volume as a rough-and-ready adherence gauge, Latham found that significantly more people with a volume above than below 100 fl reached a viral load under 50 copies/mL at three months ($P \leq 0.05$). The number of thymidine analogue mutations (TAMs) when switching to TZV/TDF, but not the 3TC-induced M184V mutation, also predicted virologic response. People with four or more TAMs (M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E) proved less likely to lower their viral load at least 10-fold at months three and six.

Latham concluded that treatment simplification may improve adherence in people with a record of adherence-related regimen failures. Simplification with TZV/TDF, she found, "may lead to renewed virological success."

A smaller study in poorly adherent people made the same point. Bernardino Roca (General Hospital of Castellon, Spain) showed that people with *comme-çi-comme-ça* compliance ("about 50 percent") to PI or NNRTI therapy can benefit from a switch to a simpler ABC-based combo [abstract 7.5/2]. Roca and colleagues monitored 41 people for three months before and six months after they switched from a PI (73 percent) or an NNRTI (27 percent), usually to TZV (76 percent). Median viral loads and CD4 counts—worsening in the last three months of PI or NNRTI therapy—had marked turnarounds when people changed to an ABC regimen (Table 2).

But swapping one antiretroviral for TDF in people already taking ABC appeared to raise the risk of virologic failure in an observational study of 96 people at Frankfurt's J.W. Goethe University clinic [abstract 9.8/4]. Annette Haberl tracked 80 men and 16 women with a viral load below 400 copies/mL for an average 397 days (range 39 to 706 days). They had a median CD4 count of 358 cells/mm^3 when they traded one drug (usually d4T, ZDV, or ddI) for TDF. Their median nadir count measured 88 cells/mm^3.

Twenty people (21 percent) saw their viral load bounce above 400 copies/mL within an average 15 weeks of the switch (range 4 to 64 weeks). People who endured a rebound had a lower nadir CD4 count (81 versus 103 cells/mm^3), a higher AIDS rate (55 percent versus 37 percent), and a shorter cumulative treatment history (44 versus 55 months). Six of 20 people (20 percent) in whom the new TDF regimen faltered added TDF to ABC, whereas nine of 76 (12 percent) with continued viral suppression added TDF to ABC.

Haberl and colleagues proposed that a triple-nuke combination including TDF and ABC "seems to promote virological failure." They warned colleagues to remain vigilant for possible failure when replacing an antiretroviral with TDF, especially in the first several weeks.

Table 2. **RNA and CD4 changes after a switch to ABC in poorly adherent people**

	Median viral load (log_{10} copies/mL)	*Median CD4 count (cells/mm^3)*
3 months before switch	3.8	287
At switch	4.2	269
3 months after switch	1.5	369
6 months after switch	0.65	358
P	<0.001	0.09

Thirty people taking a PI and 11 taking an NNRTI switched to an ABC-based regimen (TZV in 31).
Source: Bernardino Roca, abstract 7.5/2.

OTHER WAYS TO SIMPLIFY

As more once-daily and RTV-boosted PI regimens prove their mettle, clinicians can now pick from a growing menu of simpler regimens for first-line or maintenance therapy. The 9th EAC proved particularly rich on this topic, beginning with a main course of TZV studies (see preceding section) and adding a smorgasbord of once-daily options including LPV/RTV; ddI, TDF, EFV; d4T, 3TC, EFV; and 3TC, ABC, EFV. But the top attention-getter was a throwback to the late 80s—monotherapy. Only this time the lonesome antiretroviral was not ZDV but RTV-boosted LPV.

Can LPV/RTV go it alone?

LPV is not the first PI to get a serious look as stand-alone therapy. The first big randomized trial of amprenavir (APV) assigned some treatment-naive people to the unaided, unboosted PI—and it crashed.[11] But with its RTV boost, LPV is

a stronger drug than APV, immured in a resistance-resistant fortress.

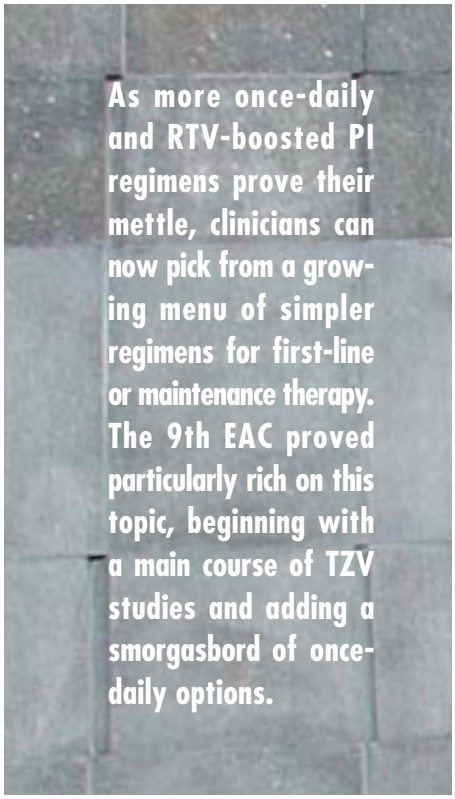
After the APV failure, the next foray into PI monotherapy came in St. Gallen, Switzerland, where Pietro Vernazza (Cantonal Hospital) treated 12 people with RTV-boosted IDV plus two NRTIs, keeping their viral load under 50 copies/mL for more than three months. Then he pulled the two NRTIs and adjusted the IDV dose in each person to keep troughs between 500 and 2,000 nM/L.[12] Defining failure as two consecutive viral loads above 400 copies/mL or three above 200 copies/mL, Vernazza saw no failures after 48 weeks of IDV/RTV. Among 138 viral load assays with a 20-copy test, 113 (82 percent) counted fewer than 25 copies/mL. Viremia blipped 25 times above 25 copies/mL.

IDV/RTV may be the ideal candidate for solo PI maintenance, Vernazza theorized, because IDV penetrates the central nervous system and genital tract well. "If all body compartments can be reached with such a high drug level," he surmised, "one active drug might suffice to suppress viral load."

Can LPV/RTV pull off the same trick? Although early research faulted LPV as a compartment penetrater, a recent study using a more sensitive assay of PI levels logged inhibitory concentrations of LPV in cerebrospinal fluid of people who adhered to standard-dose LPV/RTV.[13] LPV trough levels, like those of IDV, stay comfortably above 50 percent inhibitory concentrations for nonmutant virus when boosted by RTV. The first pilot study of solo LPV/RTV—not as maintenance after multidrug induction, but as first-line therapy in treatment-naive people—supports continued careful study. But that trial hardly makes an airtight case for LPV/RTV monotherapy.

This study involved 30 people at a single urban clinic who began LPV/RTV with fairly advanced HIV infection.[14] Their CD4 count averaged 169.5 cells/mm^3 (range 7 to 425 cells/mm^3) and their viral load 262,020 copies/mL (range 4,161 to more than 750,000 copies/mL). Twenty-one people (70 percent) began therapy with a CD4 count under 200 cells/mm^3. Joseph Gathe (Therapeutic Concepts, Houston) gave people 400/100 mg twice daily if they weighed less than 70 kg and 533/133 mg twice daily if they weighed more.

After at least 24 weeks of follow-up, only one person failed to reach a viral load below 400 copies/mL. That person had adequate LPV levels in blood and virus that remained susceptible to LPV. But eight other people dropped out of the study or had to add another drug, leaving an intent-to-treat virologic success rate of 70 percent with a 400-copy goal at 24 or more weeks. Gathe did not report how many people pared their load to below 50 copies/mL, the number one needs to compare unescorted LPV/RTV with a triple-drug LPV/RTV regimen.



In Warsaw, Gerald Pierone (AIDS Research and Treatment Center, Vero Beach, Florida) detailed a retrospective analysis of 15 people taking only LPV/RTV and a month-long prospective study of another 17 taking the boosted PI [abstract F1/5]. The chart review included four people who switched to LPV/RTV to simplify their regimen and 11 who had a virologic failure or toxicity with another regimen. After an average 82 weeks of follow-up, 11 people (including all four making the simplification switch) had a viral load below 75 copies/mL (73 percent). Two of the four people who did not attain this mark adhered poorly. The prospective study includes 17 people who wanted a one-drug regimen after controlling viremia with a standard combination. Three abandoned LPV/RTV within four weeks, while the other 14 kept their viral load below 75 copies/mL.

Weighing the merits of LPV/RTV in people with already undetectable viral loads is difficult, observed statistician Andrew Phillips (Royal Free Hospital, London), because rebounds are rare in simplification studies. One needs a large, controlled trial, Phillips said, to prove that LPV/RTV simplification works as well as continued therapy. Pierone agreed, claiming only that his work and Gathe's suggest a rationale for randomized trials.

Despite the sleek allure of RTV-boosted monotherapy, these three studies show that PI-only therapy is not a passport to freedom from toxicity or disease progression. Four people in Vernazza's pilot had kidney problems, and one succumbed to T-cell lymphoma. Two people quit Gathe's study with gastrointestinal turmoil. And nine people in Pierone's chart review needed other drugs to rein in high lipids.

Although LPV's maker, Abbott, has no financial investment in these studies, it certainly has an intellectual stake. The company is working with the US Food and Drug Administration (FDA) to plan LPV/RTV trials. Abbott surely would not risk launching such studies if it did not see a reasonable chance of success. But anyone tempted to try this tactic now must ask what's to be gained from the small but real risk of virologic failure. Would anyone in Gathe's cohort fail to clear HIV from the blood if they had started LPV/RTV with, for example, ZDV/3TC—just two more pills a day as CBV? Would there be as many side effects and unexplained dropouts if people took EFV plus CBV—three pills a day versus three or four with LPV/RTV?

Or stop the PIs and keep the NRTIs?

Steven Deeks proposed the opposite maintenance strategy in people with *detectable* viral loads—shelving the PI and continuing the NRTI [unnumbered review lecture]. He based that proposal on a study of 25 people, 18 of whom stopped a PI and kept taking NRTIs, and seven of whom dropped the NRTIs and continued a PI.

All seven who stopped their nucleosides had a fast and sustained viral rebound measuring more than a half log, even though their resistance genotype did not change over 16 weeks of follow-up. But

only three of 18 people who stopped their PI and stayed with their NRTIs had a half-log rebound during 24 weeks of follow-up.

Deeks's idea is that NRTIs alone can continue to suppress less fit resistant virus, whereas PIs can't. To shore up this hypothesis, he cited a US National Cancer Institute (NCI) study in which five people with resistant virus stopped EFV and continued ddI/d4T, while another three dropped only their d4T.[15] Viral loads did not rebound for 21 days after people stopped EFV while continuing the NRTIs. But the three people who stopped their d4T all had quick rebounds. Restarting d4T brought viral replication back under control.

But people who saw the NCI report at the Resistance Workshop and Charles Boucher (University of Utrecht) in Warsaw argued that the rebounds when stopping NRTIs do not prove those drugs continued to constrain replication of resistant virus. NRTIs kill CD4 cells, so stopping d4T in the NCI study or stopping two nukes in Deeks's study would let CD4s multiply. The sudden CD4 gush floods the circulation with fresh targets for HIV, which proliferates to make the kill. As a result, viral loads surge. That predator-prey mechanism—and not removal of antiviral pressure by NRTIs—may explain the rebounds when NRTIs stop and a PI or an NNRTI continues.

Once-daily teammates for EFV

Three studies looked at once-daily EFV-based regimens, while a fourth found a high dropout rate with TZV/EFV.

An open-label trial of once-a-day extended-release d4T (XR-d4T), 3TC, and EFV in treatment-naive people logged a 16 percent dropout rate by week 24 but good responses among people who stayed with the regimen [abstract LBF7/1]. Dushyantha Jayaweera (Jackson Memorial Hospital, Miami) reported results on 64 people who began treatment with a median CD4 count of 315 cells/mm^3 and a median viral load of 4.7 logs (about 50,000 copies/mL). The median age was 37 years, 83 percent were men, and 58 percent were non-Caucasian. The once-daily dose of XR-d4T was 100 mg for people weighing more than 60 kg and 75 mg for people weighing less.

At the 24-week mark, 10 people (16 percent) had dropped out of the study, three because of side effects (elevated alanine aminotransferase [ALT] and alkaline phosphatase, elevated lipase, and alcoholic hepatitis). The dropouts included a single virologic shortfall, defined as failure to reach or maintain a viral load below 400 copies/mL.

In a noncompleter-equals-failure analysis, 78 percent had a week-24 viral load below 50 copies/mL. In an on-treatment analysis, 94 percent nipped under the 50-copy cutoff. The median CD4-cell gain measured 134 cells/mm^3. Four people had nausea, three hypoesthesia, and two each neuropathy, diarrhea, somnolence, and vomiting.

Total cholesterol rose 17 percent during the 24 weeks, mostly as protective high-density lipoprotein cholesterol (HDL-C). The total cholesterol to HDL-C ratio fell 8 percent from baseline ($P = 0.006$). Despite the good virologic responses, adherence was not all one might hope for. Pill counts showed better than 90 percent adherence to XR-d4T and 3TC in 70 percent and to EFV in 72 percent.

An apparent advantage of XR-d4T, besides once-daily dosing, is a lighter toxic burden. Jayaweera noted that after two years of follow-up in a trial comparing XR-d4T and immediate-release d4T, the once-daily dose caused significantly less grade 2 to 4 neuropathy (4 versus 8 percent, $P = 0.005$), any lipodystrophy (11 versus 16 percent, $P = 0.05$), or lipoatrophy (8 versus 14 percent, $P = 0.004$).[16] The reason may be a 50 percent lower peak concentration with the extended-release formulation.

Piotr Pulik (AIDS Diagnostic and Therapy Center, Warsaw) found that another once-daily combination—3TC, ABC, and EFV—can work as directly observed therapy (DOT) in injecting drug users on methadone maintenance [abstract 7.3/18]. Eight of 14 people who continued treatment for 48 weeks had a viral load below 50 copies/mL and averaged a 300 CD4 cell/mm^3 gain.

The study included seven treatment-naive people and seven who had not taken antiretrovirals for six months. All had been stable in a methadone maintenance program for at least three months. Nine had AIDS. They took the antiretrovirals with their morning methadone.

Between two and 28 days after starting 3TC, ABC, and EFV, 13 of the 14 had methadone withdrawal symptoms. Pulik and colleagues jacked the average methadone dose from 79.3 mg to 94 mg. Grade 3 or 4 laboratory abnormalities (ALT, aspartate aminotransferase, amylase, and gamma-glutamyl transferase) could be attributed mostly to narcotic and benzodiazepine addictions.

One person swapped EFV for IDV/RTV because of "mood disturbance," and one traded ABC for ddI after a hypersensitivity reaction. Five people withdrew consent to continue the study for reasons not related to toxicity.

Once-daily ddI, TDF, and EFV proved to be a simple maintenance regimen in 219 people who had an undetectable viral load for at least six months while taking any regimen except TZV [abstract 7.5/16]. But the switch came with a risk of new toxicities, and three people had virologic failures within six months. None of the side effects that caused dropouts could be tied to ddI, even though TDF raises ddI levels.

Ana Barrios (Carlos III Hospital, Madrid) and coworkers at 10 other Spanish centers dosed ddI at 250 or 400 mg once daily depending on weight. Study participants had taken antiretrovirals for an average 68 months, 58 percent had hepatitis C virus (HCV) infection, and the mean CD4 count measured 578 cells/mm^3 when they switched to ddI/TDF/EFV.

The three-month follow-up included 219 people, and 127 reached the six-month mark. In intent-to-treat analyses, 85 percent at three months and 68 percent at six months kept their viral load below 400 copies/mL. Respective on-treatment response rates were 92 percent and 89 percent. The average CD4 count rose 49 cells/mm^3 in people treated for six months.

By month six 29 people (22 percent) had stopped the once-daily regimen, three because of virologic failure and 17 (13 percent) because of toxicity. Fifteen of the side effects that caused dropouts involved the central nervous system; the other two were rash and kidney dysfunction (possibly related to TDF). Five people withdrew consent, two died (one from hepatitis B virus cirrhosis), and two stopped antiretrovirals when they began treatment for HCV infection. Injecting drug users made up about half of the cohort. Switching such people to EFV may pose a higher than average risk of central nervous system side effects.

Start strong or start simple?

The first part of an induction-maintenance trial presented by Margaret Johnson

(Royal Free Hospital, London) found a relatively high dropout rate with the induction regimen, TZV/EFV [abstract F1/4]. That result should spark interest at ACTG headquarters, because the ACTG 5095 trial continues with a TZV/EFV arm and a CBV/EFV arm.

Johnson's trial—the TIME Study—enrolled 377 treatment-naive people to take TZV/EFV for 24 weeks. Then people with a viral load below 50 copies/mL are randomized to continue the four-drug regimen or to stop EFV. The cohort's age averaged 37 years, the median CD4 count measured 230 cells/mm^3 (range 19 to 940 cells/mm^3), and the median viral load stood at 4.92 logs (range 2.75 to 5.88 logs); 49 percent had a baseline viral load above 100,000 copies/mL.

After six months of TZV/EFV, only 242 people (64 percent) qualified for randomization. Fifteen people (4 percent) had a virologic failure and 73 (19 percent) quit because of side effects including:

- 34 hypersensitivity reactions
- 26 neuropsychological side effects
- 22 gastrointestinal complaints
- 11 rashes

On top of that, 18 people withdrew consent, seven had protocol violations, one had HIV disease progression, and 21 dropped out for "other" reasons. Why the high 24-week dropout rate? Johnson speculated that the large proportion of people with advanced disease may explain why so many tolerated the four-drug regimen poorly.

If she's right, an interesting question comes up: Should people with more advanced disease start with a bigger, stronger regimen to stifle HIV faster? Or should they start with a simpler and possibly more tolerable regimen? Schlomo Staszewski votes for the simpler regimen, and he has 48-week numbers from a randomized trial to back him up [abstract F1/1].

The QUAD Study pitted TZV plus SQV/RTV (1,000/100 mg twice-daily) against CBV/SQV/RTV in 59 treatment-naive people with a CD4 count below 100 cells/mm^3 (median 22 cells/mm^3 in the quad arm and 31 cells/mm^3 in the triple arm) and a median viral load of 299,000 copies/mL for the quad group and 309,000 copies/mL for the triple-therapy group. Both regimens require seven pills per dose.

In a week-48 discontinued-equals-failure analysis, between 50 and 60 percent in each group had a viral load below 50 copies/mL. In an as-treated analysis, nearly everyone had a viral load below 400 copies/mL. As in Johnson's TIME trial, large proportions of both groups had to switch one or more drugs or dropped out of the study, but rates were similar with three drugs and with four (Table 3).

Table 3. **Week-48 dropouts and switches in the QUAD study**

	CBV/SQV/RTV	*TZV/SQV/RTV*
Enrolled	30	29
On randomized treatment at week 48	18	17
Switched drugs	4	5
Discontinued	6	4
Switched drugs and discontinued	1	3
Total switches and dropouts	11	12

Source: Schlomo Staszewski, abstract F1/1.

Four RTV boost options

Three trials reviewed in Warsaw sized up RTV-boosting strategies—with SQV, LPV (once or twice daily), and IDV (at 400 mg twice daily).

Mike Youle (Royal Free Hospital, London) laid out the final results from MaxCmin2, an open-label trial that randomized naive or experienced people to take standard-dose LPV/RTV or (soft-gel) SQV/RTV at 1,000/100 mg twice daily [abstract F11/3]. Clinicians picked NRTIs or NNRTIs for the regimen before randomization. (MaxCmin1, all will recall, found equivalent efficacy with IDV/RTV and SQV/RTV, but more toxicity in the IDV arm.[17])

MaxCmin2 participants started with a median CD4 count of 240 cells/mm^3 and a median nadir of 100 cells/mm^3. Half entered the trial with no PI experience, 30 percent had a PI failure on their charts, and 20 percent couldn't tolerate an earlier PI. Among 163 people who started LPV/RTV, 22 (13 percent) had to switch at least one drug, while 47 of 162 (29 percent) who started SQV/RTV needed a switch ($P = 0.001$). Most discontinuations involved gut problems, more often with SQV/RTV.

A week-48 intent-to-treat (exposed) analysis found a significantly higher risk of virologic failure in the SQV/RTV arm (about 35 percent) than in the LPV/RTV arm (about 20 percent) ($P = 0.0006$). But a week-48 on-treatment analysis showed similar proportions in each group—75 percent on SQV and 70 percent on LPV—with a viral load below 50 copies/mL ($P = 0.36$). As a result, Youle proposed that the higher failure rate in the SQV/RTV arm does not reflect a difference in the intrinsic potency of these regimens, but a difference in tolerability. Rates of disease progression (12 with SQV/RTV and seven with LPV/RTV) and death (five with SQV/RTV and none with LPV/RTV) appeared to favor the LPV arm. But Youle believes those differences may mean as much as a roll of the dice because of the small numbers.

Twice-a-day LPV/RTV continues to hold its own against—or to outperform—other regimens. But can it work as well once daily? Twenty-four-week results of a randomized study that enrolled 120 treatment-naive people suggest that it can [abstract F1/3]. Daniel Podzamczer (Hospital de Bellvitge, Barcelona) and colleagues in the United Kingdom, the United States, and Singapore randomized 115 people to take 800/200 mg of LPV/RTV once daily and 75 to take the twice-a-day dose. Everyone also took TDF and emtricitabine (FTC) once daily. The once-daily group started with a median CD4 count of 214 cells/mm^3 and a median viral load of 4.8 logs. In the twice-daily group those numbers were 232 cells/mm^3 and 4.6 logs.

Both groups lost 16 percent of enrollees by week 24 because of side effects (11 percent with once-daily LPV and 3 percent with twice-daily LPV), loss to follow-up, and withdrawn consent. Whereas 5 percent in the twice-daily group had diarrhea, 12 percent on the once-daily regimen did, but that difference lacked significance. In a week-24 missing-data-equal-failure analysis, 57 percent in both arms had a viral load below 50 copies/mL. In an on-treatment analysis, sub-50 rates were 68 percent once daily and 70 percent twice daily. Those percentages climbed among people with 32 weeks of follow-up. Podzamczer and colleagues have seen no virologic failures so far.

Jade Ghosn (Pitié-Salpêtrière Hospital, Paris) and colleagues tested another slimmed-down RTV-boosted regimen, IDV/RTV 400/100 mg twice daily, in 47 people switching from another IDV dose and in 40 starting 400/100 mg as part of their first regimen [abstract 7.5/4].

In a 20-person pharmacokinetic study, IDV trough concentration in the switch group rose significantly by week four while the peak concentration fell significantly ($P < 0.001$ for both). No one had an IDV trough below 120 ng/mL, a level linked to virologic failure. All 47 people who switched from unboosted IDV or from a higher boosted IDV dose maintained a viral load below 200 copies/mL for 48 weeks, but two people dropped the PIs because of side effects. No one who tolerated IDV at 800 mg three times daily had toxicity problems with the 400/100-mg dose.

The first-line study involved 40 people with a median CD4 count of 84 cells/mm^3 (range 3 to 558 cells/mm^3) and a median viral load of 230,957 copies/mL (range 5,000 to 750,000 copies/mL). By week 48 the median CD4 count had climbed to 252 cells/mm^3 and the median viral load had shed 3.83 log copies/mL. In a 48-week on-treatment analysis, 96 percent had a viral load under 400 copies/mL. Ghosn tallied eight grade 3 or 4 toxicities, including gastrointestinal gyrations, diabetes, xerosis, arthralgia, elevated creatinine, and hemolysis. Eight people stopped IDV/RTV because of side effects.

CD4-GUIDED DRUG BREAKS

Surely the easiest way to simplify antiretroviral therapy is to stop it. Alas, that strategy has yet to yield a clinical benefit in people quitting treatment for primary infection or chronic infection, or before salvage. Although the GIGHAART study of presalvage drug breaks[18] found a 12-week virologic advantage—but no clinical pluses—a similar study by the same group underscored the grave dangers of suspending treatment in people with low CD4 counts [abstract 7.4/10, see "REVERSE reverses presalvage STI hopes" below].

The one strategic treatment interruption (STI) tactic that seems to be working is a drug break guided by a person's CD4 count. When the count drifts down to a preset mark, therapy resumes. Three studies presented in Warsaw probed for clues to safely steering STIs by CD4 count. As in most previous studies, CD4-signaled breaks lasted longest in people with higher CD4 nadirs. Pretreatment and on-treatment viral load also sometimes augured longer STIs.

In a multicenter observational study, Cristina Mussini (Clinic of Infectious Diseases, Modena, Italy) isolated three factors that independently predicted a longer CD4-guided holiday:

- Higher CD4 nadir: adjusted relative hazard (ARH) 0.68 (95 percent confidence interval 0.50 to 0.92) per 100 cells/mm^3 higher, $P = 0.01$
- More than 12 months (versus 0 to 12 months) with viral load below 50 copies/mL: ARH 0.08 (0.03 to 0.25), $P = 0.0002$
- Lower viral rebound after treatment interruption, ARH 1.95 (1.17 to 2.23), $P = 0.01$

The 140 people studied needed a nadir CD4 count above 250 cells/mm^3, a current CD4 count above 500 cells/mm^3, and at least 12 months of therapy. The viral load could be above or below 50 copies/mL, and drug breaks had to last at least four weeks. Study participants had a high median pretreatment CD4 count of 410 cells/mm^3 (interquartile range 347 to 523 cells/mm^3) and a robust pre-STI median of 804 cells/mm^3 (interquartile range 674 to 1,031 cells/mm^3). Sixty percent had a viral load below 50 copies/mL when they stopped their antiretrovirals, one third of them for 12 months or more. People had to resume treatment if their CD4s dipped below 350 cells/mm^3; they could also resume whenever they felt the need.

At the time of Mussini's report, 75 people (54 percent) remained off treatment, 34 (24 percent) restarted because they toed the 350-cell tripwire, and 31 (22 percent) wanted to resume treatment before their CD4 count nosed under 350 cells/mm^3. The median time to reaching one of those endpoints measured 104 weeks.

Mussini concluded that people with a CD4 nadir above 350 cells/mm^3, a viral load below 50 copies/mL for more than 12 months, and a low viral rebound when interrupting treatment can safely stop therapy for long stretches. Even in this group, with its zesty median CD4 nadir of 410 cells/mm^3—well above the mark where most people in rich countries now start therapy—one person endured an AIDS diagnosis during the study: Kaposi's sarcoma.

In a smaller cohort with similar CD4 nadirs and similar on-treatment CD4 counts, pre-HAART CD4 count proved an independent predictor of the need to restart therapy [abstract 7/6.5]. In a univariate comparison of restarters and long-term interrupters, nadir CD4 count emerged as a (nearly significant) discriminator.

Laurent Cotte (Hôtel-Dieu, Lyon, France) monitored 41 asymptomatic people who had a CD4 count above 350 cells/mm^3 when they started a potent regimen and a viral load under 50 copies/mL for the preceding year. They had to restart therapy if an HIV symptom appeared or if their CD4 count edged under 350 cells/mm^3. Thirteen people had taken one- or two-drug therapy before starting HAART. Pretreatment CD4 counts averaged 489 cells/mm^3 (±132 cells/mm^3), pre-HAART CD4 counts 541 cells/mm^3 (±155 cells/mm^3), and pre-STI CD4 counts 782 cells/mm^3 (±231 cells/mm^3).

The median STI lasted 16 months, and nine people (22 percent) had to resume treatment because their CD4 count slipped below the 350-cell mark—almost exactly the same percentage as in Mussini's study. Also as in Mussini's study, a lower CD4 nadir signaled the need to resume therapy, as did four other factors (Table 4). In several logistic

Table 4. **Univariate factors predicting need to restart therapy**

	Restart therapy (n = 9)	*Continue STI (n = 32)*	*P*
CD4 nadir (cells/mm^3)	366 ± 90	457 ± 130	0.057
Pretreatment CD4 count (cells/mm^3)	417 ± 109	509 ± 155	0.063
Pre-HAART CD4 count (cells/mm^3)	442 ± 113	570 ± 155	0.027
CD4 count in year before STI (cells/mm^3)	654 ± 174	818 ± 234	0.057
Pretreatment viral load (log copies/mL)	5.0 ± 0.9	4.3 ± 0.8	0.06

Source: Laurent Cotte, abstract 7.6/5.

Table 5. **Effect of nadir CD4 count on STI duration**

Nadir CD4 count	*n*	*Length of first STI (months)*
All patients	31	9.5 (2 to 40)
<200 cells/mm^3	5	2.3 (2 to 8.8)
200 to 350 cells/mm^3	15	9 (2.3 to 34)
>350 cells/mm^3	10	19.8 (9.3 to 40)

Source: Andrea Boschi, abstract 7.6/3.

regression models, only a lower pre-HAART CD4 count predicted the need to restart therapy ($P = 0.011$). One person had to restart treatment because of the acute retroviral syndrome and one because herpes zoster broke out seven months into the STI.

Nadir CD4 count also foretold how long STIs lasted in a study of 31 people by Andrea Boschi (AUSL, Rimini, Italy) [abstract 7.6/3]. Everyone had a CD4 count above 500 cells/mm^3, then stopped treatment because of antiretroviral toxicity or failure, or because the patient and physician thought an STI made sense. People had to restart therapy if their CD4 count approached 200 cells/mm^3, if they had a new AIDS symptom, or if they became pregnant. They could also restart any time they felt the urge.

The median CD4 nadir stood at 308 cells/mm^3 but ranged widely from 30 to 800 cells/mm^3. When the group stopped treatment, the median CD4 count measured 737 cells/mm^3 (range 507 to 1,777 cells/mm^3). Over 12 to 51 months of follow-up (median 21.5 months), 14 people took two STIs, 10 took three STIs, and one took four STIs. Oral candidiasis cropped up in one person during two STIs, and one person had the acute retroviral syndrome during the first STI but not during later breaks.

In a linear regression analysis that included age, gender, risk for HIV infection, nadir CD4 count, CD4 count at STI, pretreatment viral load, duration of therapy, and duration with a viral load below 50 copies/mL, only nadir CD4 count stood out as an independent predictor of STI length ($P = 0.001$) (Table 5). The CD4 count when the drug break began did not affect STI length, Boschi found, because CD4 gains on treatment correlated inversely with CD4 loss during the drug break, as other researchers have reported.[19] The CD4 cells therapy adds back apparently lack the staying power of the CD4s one starts with.

What can one make of these results? The link between lower CD4 nadir and a quicker restart of antiretrovirals held true from study to study. But what nadir should be judged a safe threshold? Boschi and colleagues, who tracked people with nadirs ranging from 30 to 800 cells/mm^3 and who included people stopping treatment because of virologic failure, settled on 200 cells/mm^3 as a safe nadir. Mussini, who studied people with nadirs usually above 350 cells/mm^3, proposed that as the cutoff.

Mussini suggested that it's better to start antiretrovirals with a higher versus a lower CD4 count, then to take a long drug break, knowing that one can restart the same regimen when too many T cells vanish. In Mussini's eyes the alternative—starting treatment at a lower count then possibly having to switch regimens because of failure—is less attractive. The counterargument is that most untreated people with 347 to 523 cells/mm^3—the interquartile pretreatment range in Mussini's cohort—can afford to wait a few years before taking antiretrovirals, in the reasonable hope that the regimens of 2006 will be stronger and safer than those of today.

None of the studies found that a higher CD4 count when the STI began independently prefigured a longer time off treatment. And all of them chronicled a small risk of clinical progression or the acute retroviral syndrome.

No matter what studies like this find, people who feel well—except for drug side effects—will continue to push for drug holidays. Gerd Klausen (Praxiszentrum Kaiserdamm, Berlin) and fellow Berlin clinicians gave colleagues a retrospective look at what happens when 241 people opt to stop treatment with their doctors' acquiescence [abstract F11/2]. At this point readers will not be surprised to learn that people with low CD4 nadirs took the shortest breaks. Klausen also reported shorter drug breaks in people with high pretreatment viral loads. Although the Berlin clinicians recorded not one opportunistic infection during the drug breaks, they found that CD4 counts and viral loads returned sluggishly to pre-STI levels after therapy resumed.

Klausen's analysis included everyone who quit therapy because of side effects, adherence problems, or "drug fatigue" between July 2000 and July 2002. Follow-up lasted through December 2002. Though the average time since HIV diagnosis measured 7.4 years, treatment duration averaged only 3.7 years.

The mean pretreatment CD4 count was what one would expect in Western Europe, 283 cells/mm^3, while the average pre-HAART viral load had climbed well above 5 logs—to 222,000 copies/mL. The group stopped treatment at a median viral load of 7,525 copies/mL, with 59 percent under 50 copies/mL and another 15 percent between 50 and 1,000 copies/mL. The pre-STI CD4 count averaged 585 cells/mm^3, with 7 percent under 200 copies/mL.

Hepatitis flares when stopping 3TC

Interrupting or switching 3TC-containing regimens can be particularly problematic in people coinfected with hepatitis B virus (HBV) because withdrawing 3TC may reactivate HBV. Manuel del Rio (Son Dureta Hospital, Palma de Mallorca, Spain) offered a cautionary reminder with two case reports [abstract 7.6/6].

The first case involved an HBV-coinfected 38-year-old man taking a 3TC-containing regimen for the preceding four years. Liver enzymes had remained normal during 3TC therapy. Failure to control HIV prompted a switch to a regimen that did not include 3TC. Two months later this man sought care because of weakness and jaundice. His clinicians diagnosed acute hepatitis with hyperbilirubinemia and recorded significant elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Liver function tests returned to normal when 3TC therapy resumed.

A 31-year-old man coinfected with HBV and HCV stopped a 3TC regimen because of confirmed resistance. Five months later he had to be admitted to the hospital because of jaundice and right upper quadrant pain. His clinicians detected serologic markers of HBV reactivation and restarted 3TC, whereupon symptoms and lab abnormalities resolved.

These findings reflect a report on the Dutch ATHENA cohort, in which the risk of liver toxicity rose among HBV-coinfected people stopping 3TC.[20]

Del Rio advised colleagues to check for HBV status when considering dropping 3TC. People in whom 3TC has apparently controlled HBV should retain the nucleoside or should have close liver function monitoring. The Dutch recommend keeping 3TC even in people with resistance to the drug.

At the time of Klausen's report, 60 percent had restarted therapy, and the average STI lasted only 4.9 months.

During the drug breaks viral loads rose an average 15,000 copies/mL monthly in people with a pretreatment load under 30,000 copies/mL versus nearly 60,000 copies/mL monthly in people with more than 100,000 copies/mL before starting therapy. The average load gained about 30,000 copies/mL monthly in people with a CD4 nadir above 200 copies/mL, compared with more than 50,000 copies/mL monthly in those with a sub-200 nadir.

Fewer people with a CD4 nadir above 500 cells/mm^3 or a pretreatment load below 30,000 copies/mL had to restart treatment when compared with those with lower nadirs and higher pretreatment loads. Large majorities of those with a pretreatment load above 100,000 copies/mL (75 percent) or a nadir below 200 cells/mm^3 (85 percent) had resumed therapy.

Three months after 89 people restarted therapy, 55 percent had reached their pre-STI CD4 count and 66 percent a viral load under 50 copies/mL. Respective percentages 12 months after ending drug holidays were 75 percent and 84 percent.

Table 6. **Comparison of STI groups in four presalvage trials**

Trial and first author	*Site*	*Design*	*n with STI*	*Baseline CD4 cells/mm^3*	*STI length (m)*	*Surrogate endpoints*	*Clinical endpoints*
CPCRA 064, Lawrence	United States	Randomized	138	Median 153 (range 52 to 281)	4	CD4s significantly lower in STI group for 4 months after resuming therapy	2.57 times higher risk of progression in STI group
Retrogene, Ruiz	Spain	Randomized	22	Median 383 (range 84 to 783)	3	No CD4 or viral load difference from no-STI group after 48 weeks	
GIGHAART, Katlama	Paris	Randomized	34	Median 26	2	21 of 34 (62%) reached primary endpoint of ≥1-log viral load drop at week 12	Progression in 8 of 34 (24%) vs 7 of 34 (21%) in the non-STI group
REVERSE, Ghosn	Paris	Single arm	23	Median 43 (range 1 to 372)	2.7 to 8.7	1 of 23 (4%) reached primary endpoint of ≥1-log viral load drop at week 12	Progression in 15 of 23 (65%)

Sources: Jodi Lawrence,[1] Lidia Ruiz,[2] Christine Katlama,[18] Jade Ghosn, abstract 7.4/10.

STIs—PAST AND FUTURE

The 9th EAC featured two studies that may demarcate the past and the future of STIs. The view to the past came in another presalvage STI study by Christine Katlama's group at the Pitié-Salpêtrière Hospital in Paris [abstract 7.4/10]. Analyzing this trial and similar recent studies, the group's statistician, Dominique Costagliola, called it "a complete disaster" [abstract F7/5]. A small, uncontrolled study of STIs in children, on the other hand, may have opened a portal to the future. Which group of people with HIV, after all, seems a more likely candidate for treatment breaks than children facing 50, 60, or 70 years of antiretroviral therapy? If anyone needs time off, they do.

How long can STIs last in kids?

Antoni Noguera (University of Barcelona) reported results of 11- to 45-month STIs in nine vertically infected children, all of whom had a viral load below 50 copies/mL and a CD4 percent above 25 percent while taking their first HAART regimen [abstract F10/4]. None had resistance mutations or HIV-related symptoms. Children and parents agreed to restart therapy in the face of the acute retroviral syndrome, clinical progression, or a CD4 tally below 17 percent or 350 cells/mm^3.

The group included three children first treated before they were eight weeks old and nine first treated after they were two years old. The younger group had taken antiretrovirals for 26 to 51 months and had maintained a viral load below 50 copies/mL for two to 48 months. The older group had taken HAART for 49 to 61 months and had kept a cap on replication for 28 to 62 months. So these children had very well-controlled infection.

Eleven to 45 months after stopping therapy, none of the children has touched an antiretroviral. CD4 percents in the three younger children ranged from 29 to 55 percent, while their viral loads ranged from 3.1 to 4.8 log copies/mL. In the nine older children, CD4 percents ranged from 17 percent (437 cells/mm^3) to 45 percent and viral loads from 4.0 to 5.6 log copies/mL.

Treatment-induced body fat changes appeared to improve in some children, and other toxicities resolved. Noguera said all children and their families are satisfied with the results so far. PENTA, the European pediatric HIV trials group, plans to study CD4-guided STIs in children with a viral load below 50 copies/mL and a CD4 percent above 30 percent. If children in that trial manage to go one to four years without antiretrovirals, as in Noguera's pilot study, they will reap one to four years of near-normal childhood.

Who sees that elephant in the living room?

For adults with multidrug-resistant virus, the future of STIs is not so bright. Two recently published randomized studies of presalvage STIs showed either no benefit[2] or a bigger risk of disease progression[1] in groups assigned to take a drug break intended to resensitize resistant virus to the rescue regimen (Table 6). The latest presalvage STI study, Katlama's nonrandomized REVERSE trial, supported results of the largest such study, CPCRA 064,[1] in documenting a high risk of virologic, immunologic, and clinical failure with this strategy.

Perhaps the most telling finding in REVERSE is that drug-sensitive virus overwhelmingly replaced drug-resistant virus during the extended STI. But as in earlier studies,[1,2,21,22] resurrection of susceptible virus proved no salvation for STI takers. Earlier studies establish the reason: undetectable minority pockets of resistant virus empty into the circulation as soon as drug pressure starts picking those pockets. Perhaps REVERSE, along with these earlier

trials, will bury forever the notion that a majority population of drug-susceptible virus means anything at all to salvage success when minority mutant virus remains holed up and ready to roar back.

Those still hoping this strategy will work for some may want to wait for results of Katlama's 2004 trial in which compact therapy versus mega-HAART will follow an eight-week presalvage STI. Those blessed with more patience can look forward to the four-year, four-arm OPTIMA trial, which is testing a presalvage break versus immediate salvage with either mega-HAART or a simpler regimen. In the meantime, the evidence against stopping drugs in people with advanced HIV infection seems as flagrant as the elephant in the living room, though perhaps just as easy to ignore.

REVERSE reverses presalvage STI hopes

Jade Ghosn in Katlama's group reported that REVERSE enrolled 23 people with a median CD4 count of 43 cells/mm^3 (range 1 to 372 cells/mm^3) and a median viral load of 134,000 copies/mL (range 32,000 to 490,000 copies/mL) [abstract 7.4/10]. Those numbers come close to baseline values in GIGHAART's STI arm[18]—26 cells/mm^3 and 5.4 logs (about 250,000 copies/mL). As in GIGHAART, REVERSE participants took a megadrug regimen (three or four NRTIs, one NNRTI, and three PIs with or without hydroxyurea or ENF) when they resumed therapy.

But REVERSE differed from GIGHAART in one pachydermic detail: the GIGHAART drug break lasted eight weeks; in REVERSE people abstained from antiretrovirals until virus resistant to two or more classes reverted to wild-type, that is, until three or more thymidine analogue mutations (TAMs), all NNRTI mutations, and three or more primary protease mutations dropped out of view. Treatment breaks lasted 82 to 262 days, during which the median CD4 count slumped by 30 cells/mm^3 and the median viral load rose 0.54 log.

Seventeen of the 23 enrollees had virus susceptible to no current antiretroviral. They had a median of five TAMs (which include M41L, D67N, K70R, L210W, T215Y/F, K219Q/E), three primary protease mutations, and two non-nucleoside mutations. After the STIs, Ghosn and colleagues counted a median of two TAMs, no primary PI mutations, and no NNRTI mutations.

Table 7. **Mutations* and active drugs† in GIGHAART and REVERSE**

	Major PI mutations	*All PI mutations*	*NNRTI mutations*	*NRTI mutations*
GIGHAART day 0	2	7	2	5
GIGHAART after STI	2	7	2	5
REVERSE day 0	3	9	2	6
REVERSE after STI	0	2	0	2
	Taking 0 active drugs	*Taking 1 active drug*	*Taking 2 active drugs*	*Taking ≥3 active drugs*
GIGHAART day 0	10%	50%	25%	12%
GIGHAART after STI	5%	25%	31%	33%
REVERSE day 0	45%	31%	12%	9%
REVERSE after STI	9%	5%	12%	71%

*Medians.

†Active according to the ANRS genotypic resistance algorithm.

Source: Dominique Costagliola, abstract F7/1.

One of 23 people (4 percent) met REVERSE's primary endpoint, at least a 1-log drop in viral load after 12 weeks of megasalvage. The median CD4 count did not return to baseline after 12 weeks of therapy, but drug-resistant virus reemerged. The most unwelcome outcome reflects results of the CPCRA study[1]—15 of 23 people (65 percent) picked up a new AIDS diagnosis, many of them nasty: eight cases of *Candida* esophagitis and one each of lymphoma, pulmonary Kaposi's sarcoma, *Pneumocystis carinii* pneumonia, progressive multifocal leukoencephalopathy, disseminated *Mycobacterium avium* complex, wasting, and cytomegalovirus colitis.

Unfortunately, the 9th EAC's organizers did not select this salient study for a slide talk. But they did hand the microphone to Dominique Costagliola (Pierre and Marie Curie University, Paris), who had the unenviable task of delivering a talk called "Treatment interruption in patients with multiple failures to ARV therapy: Can the controversy be solved?" Reviewing results of REVERSE and the three controlled trials of this tactic,[1,2,18] one might be excused for answering with a quick "yes—presalvage STIs don't work." But Costagliola took the view that GIGHAART's drug break did work, then proceeded to compare that trial with REVERSE.

Median numbers of major baseline mutations were similar in the two trials (Table 7). But after GIGHAART's eight-week drug break, those medians stood at precisely the same point. (Despite that finding, curiously, taking a drug break plus reversion of resistant virus to wild-type raised the 12-week chance of virologic success 12.4 times compared with the control group in GIGHAART.[18]) After the 82- to 262-day drug breaks in REVERSE, the median number of resistance mutations dropped dramatically. Both studies had the same primary endpoint—the percentage of people with at least a 1-log drop in viral load 12 weeks after starting a megasalvage regimen. In GIGHAART 62 percent cleared that hurdle, in REVERSE 4 percent. Those findings reinforce the conclusion that reversing resistance mutations helps not a bit before industrial-strength salvage.

Costagliola also showed that the number of "active" drugs after the STI—defined genotypically according to the ANRS algorithm—had no impact on 12-week virologic salvage success (Table 7). The median number of active drugs in GIGHAART measured 2.4 ± 2.0, the median in REVERSE 4.9 ± 2.7. Slightly more than 30 percent in GIGHAART had virus sensitive to three or more drugs after their break, compared with more than 70 percent in REVERSE. These numbers should be no surprise—when sensitivity is defined as lack of detectable resistance mutations in people with mine-deep antiretroviral experience. The mutations are still there; the assay just can't dig deep enough. So the drugs Costagliola defined as active were, in fact, not.

As earnest as this attempt was to draw some lessons from presalvage STI studies, the exercise was probably as bootless. Why? Because the primary endpoint of GIGHAART and REVERSE—the percentage of participants with a 12-week viral load drop of at least 1 log—a mere 10-fold—is not what matters when shell-shocked antiretroviral veterans take aim with yet another regimen. What matters is how much longer they last without another

AIDS diagnosis, and how much longer they survive. In REVERSE, 15 people (65 percent) added another AIDS diagnosis to their charts during the study, hardly a surprise when the median CD4 count dropped from 43 to 13 cells/mm^3 during the STI and did not get back up to 43 cells/mm^3 after treatment resumed.

The GIGHAART break takers may have enjoyed bigger viral load drops and CD4 gains after they started their salvage regimens than the nonbreak group. But they did no better than the control group in warding off AIDS. Costagliola reported eight new AIDS diagnoses in GIGHAART's STI group (24 percent) and seven (21 percent) in the control group. Two people in both groups had died when Katlama reported results earlier in 2003.[18] By the endpoints that mean most—health- and life-ending endpoints—presalvage STIs didn't work in GIGHAART either.

OTHER SALVAGE OPTIONS

If presalvage STIs don't work (see preceding section), what is one to do for people with thick treatment histories? The most reasonable answer seems to be the one proposed by the British HIV Association[8]—keeping the CD4 count as high as possible. And that means continuing, not stopping, treatment.

Dominique Costagliola, who analyzed the REVERSE and GIGHAART STI trials in Warsaw (above), also offered refreshing evidence that treatment options have improved in recent years for people with triple-class failure [abstract F7/1]. And in this analysis of the French Hospital Database on HIV, the endpoints were hard—a new AIDS disease or death. The good news is that progression rates dropped steadily from 1998 to 2001, and they appeared to do so because of four drugs that first saw wide use in those years—LPV, APV, ABC, and TDF.

The cohort included 1,092 people who had taken at least two NRTIs, two PIs, and one NNRTI, yet had a viral load above 5,000 copies/mL before changing therapy from 1998 through 2001. They had a median CD4 count of 181 cells/mm^3, a median viral load of 71,009 copies/mL, a median five years of antiretroviral experience, and exposure to a median of nine antiretrovirals.

Over a median 13 months of follow-up, 187 people added a new AIDS diagnosis or died. The crude progression rate fell according to the year when people entered the cohort:

- 20.1 per 100 patient-years in 1998
- 15.1 per 100 patient-years in 1999
- 11.1 per 100 patient-years in 2000
- 8.6 per 100 patients-years in 2001

After statistical adjustment for baseline variables, this steady decline proved highly significant ($P < 0.001$). In a multivariate Cox model adjusting for baseline CD4 count and viral load, AIDS status, transmission group, number of previous antiretrovirals, and treatment change during follow-up, the risk of progression dropped 50 percent from 1998 to 1999, 60 percent from 1998 to 2000, and 70 percent from 1998 to 2001.

But when Costagliola rejiggered the model to include new drugs added at baseline, year of cohort entry lost its significant effect on progression. In other words, the drugs themselves—not some temporal factor—drove the drop. In the new model, use of the four drugs correlated with at least a 1-log drop in viral load and at least a 50-cell/mm^3 rise in CD4 count.

New antiretrovirals remain imperfect, and the best new regimen one can concoct will not rescue everyone with resistant virus. But it is impressive that the arrival of new drugs since 1998—two years into the HAART era—continues to drive down morbidity and mortality.

ATV versus LPV after PI failure

Analysis of a trial pitting once-daily atazanavir (ATV) against twice-daily LPV in PI-experienced people found better responses with LPV than with unboosted ATV [abstract F7/2]. In a match-up between RTV-boosted ATV (300/100 mg once daily) and standard-dose LPV/RTV, response rates began to drop sharply in both groups when people had four or more major PI mutations at baseline. Even so, the response to LPV/RTV proved slightly but consistently better than the response to ATV/RTV with three, four, or five or more baseline PI mutations.

Carlos Zala (Fundacion Huesped, Buenos Aires) reviewed results from BMS study 043 (unboosted ATV versus LPV in 158 people with PI experience) and BMS study 045 (boosted ATV versus LPV in 151 people in whom at least one PI, one NNRTI, and one NRTI had failed). In the 043 study, 72 percent randomized to ATV had virus susceptible to the PI according to the ViroLogic assay, and 86 percent in the LPV arm had LPV-susceptible virus. Similar proportions in the two groups—26 percent on ATV and 23 percent on LPV—had four or more PI mutations.

After 24 weeks of treatment, people with four PI mutations at baseline averaged close to a 2-log (100-fold) drop in viral load if they took LPV/RTV, but only a little more than a 1-log (10-fold) drop with unboosted ATV. Even people with five or more PI mutations at baseline averaged a 2-log viral load decline with LPV/RTV versus slightly more than a 1-log dip with ATV. The comparison is limited, Zala observed, by the small numbers of people with four or five baseline PI mutations (20 taking ATV and 23 taking LPV/RTV).

In the 045 study comparing ATV/RTV with LPV/RTV, 74 percent randomized to ATV and 77 percent randomized to LPV had virus susceptible to those PIs at baseline on the ViroLogic assay. In the ATV arm, 33 percent had more than four PI mutations at baseline, compared with 37 percent in the LPV arm.

After 24 weeks of treatment, LPV takers with three baseline PI mutations averaged about a 2-log drop in viral load, while the ATV group averaged only a slightly lower drop. Among people starting LPV with four PI mutations, the viral load drop averaged about 1.5 logs, and among those starting with five or more mutations, about 1.25 logs. Responses in the ATV arm slightly lagged those declines. Although these differences between responses to LPV/RTV and ATV/RTV lacked statistical significance, LPV performed consistently better in people with two or more baseline mutations. Again, the numbers in all these subanalyses were small.

The two studies show, though, that boosted ATV easily betters unboosted ATV in people with PI experience. Both ATV/RTV and LPV/RTV begin to lose their punch in people with heavy treatment experience, as in study 045, and with four or more baseline mutations. In people with less PI experience, study 043 suggests, LPV/RTV retains more activity against virus with four or five PI mutations.

RTI-sparing salvage with triple-PI regimens

Three studies reported in Warsaw tested

Table 8. **Responses to triple-PI, RTI-sparing salvage regimens**

First author	*Site(s)*	*Regimen*	*n*	*n at week 24*	*24-week response*	*Comments*
Laurenroth-Mai	Germany	LPV/RTV ± IDV (666 mg bid) (± NNRTI ± TDF)	38	27	17 of 27 (63%) <50 copies/mL	Response worse with IDV or LPV experience or baseline load above 100,000 copies/mL. Adding NNRTI or TDF did not improve response.
Dauer	Frankfurt	LPV/RTV + IDV (800 mg bid)	44	19	12 of 19 (63%) <400 copies/mL	Three people started with lower PI doses and eight had dose reductions. Eleven stopped because of toxicity and seven because of virologic failure.
Delassus	France	LPV/RTV + SQV (1,000 mg bid)	18	18	14 (78%) with at least a 1-log drop in viral load; 10 (55%) <50 copies/mL	No genotypic resistance to LPV or SQV at baseline, and none emerged during the study.

Sources: Elke Laurenroth-Mai, abstract 7.4/2, Brenda Dauer, abstract 7.4/4, and Jean-Luc Delassus, abstract 7.4/12.

the merits of LPV/RTV plus a third PI without NRTIs and usually without NNRTIs. Two groups tested IDV as the third PI and one sized up SQV in people with intolerance or resistance to reverse transcriptase inhibitors.

A group of German clinicians headed by Elke Laurenroth-Mai (Private Practice, Berlin) had good results combining standard-dose LPV/RTV with 666 mg of IDV twice daily in 38 heavily pretreated people, 36 of them with PI experience (Table 8) [abstract 7.4/2]. Adding an NNRTI in people without NNRTI experience or TDF in people with a favorable resistance profile did not improve responses. People who had tried IDV or LPV earlier, and those with a viral load above 100,000 copies/mL, fared worse with the triple-PI regimen.

Study participants had taken a median of four regimens over a median of 5.4 years. Thirty-six (95 percent) had used a PI, eight (21 percent) LPV and 15 (40 percent) IDV. Sixteen of 32 people with a baseline genotype (50 percent) had five or more PI mutations. The median starting viral load stood at 40,900 copies/mL (range 1,000 to 250,000 copies/mL) and the median CD4 count at 295 cells/mm^3 (range 12 to 877 cells/mm^3).

Four people dropped out at week 12 because of side effects (three retinoid symptoms and one visceral fat accumulation), despite reaching a viral load below 50 copies/mL. Other side effects, including gastrointestinal upsets and itchy skin, often resolved or responded to indinavir dose reduction. Median triglyceride levels jumped by 66 mg/dL by week 24, while median total cholesterol rose 60 mg/dL.

At week 12 the IDV trough averaged 578 ng/mL (range 204 to 1,065 ng/mL) and the LPV trough 5,290 ng/mL (range 1,950 to 9,213 ng/mL). Laurenroth-Mai and colleagues trimmed the IDV dose to 400 mg twice daily in five people with a trough above 750 ng/mL and upped the dose to 999 mg twice daily in three people with a trough under 450 ng/mL. Follow-up drug level monitoring in these people confirmed troughs between 500 and 750 ng/mL.

A week 12 on-treatment analysis showed a median 2.92-log drop in viral load, which held through week 24 in people who continued treatment. Twenty-two of 35 people (63 percent) had a week 12 viral load below 50 copies/mL, as did 17 of 27 (63 percent) at week 24. The median CD4 count rose 137 cells/mm^3 in virologic responders and almost as well—128 cells/mm^3—in virologic nonresponders.

Nineteen of 20 people with a baseline load below 100,000 copies/mL had at least a 2-log drop in viral load at week 24, compared with three of seven who started salvage with a higher baseline load. Four other factors predicted a good 12-week virologic response:

- Baseline CD4 count: 331 cells/mm^3 in responders versus 187 cells/mm^3 in nonresponders
- Baseline PI mutations: four versus seven
- IDV experience: 26 percent versus 100 percent
- LPV experience: 15 percent versus 50 percent

The same three PIs, but with no reverse transcriptase inhibitors, boosted CD4 counts and controlled viral replication reasonably well in 44 people in the Frankfurt HIV Cohort studied by Brenda Dauer [abstract 7.4/4].

Most people in the Frankfurt group started with a higher IDV dose than in Laurenroth-Mai's study—800 mg twice daily. But dose adjustments also proved common in Frankfurt. One person started with 400 mg of IDV twice daily because of earlier intolerance, and one started with 666 mg twice daily because of low weight. Another person began with 266/66 mg of LPV/RTV twice daily because of earlier intolerance. Dauer and colleagues lowered the twice-a-day IDV dose to 666 mg in five people and to 400 mg in two, while easing the LPV/RTV dose to 266/66 mg twice daily in another two. Reasons for the reductions were high plasma levels on day 14, intolerance, and pill burden.

The cohort had taken antiretrovirals for a median of 6.9 years (range 0.6 to 13.7 years), trying a median of 10.5 antiretrovirals, including 3.5 PIs. The median number of PI mutations at baseline was two, ranging from none to nine. The presalvage median load stood at 5.0 logs (range 1.7 to 6.0 logs) and the median CD4 count at 125.5 cells/mm^3 (range 4 to 516 cells/mm^3).

Twenty-two people (50 percent) have stopped the three-PI regimen, 11 because of intolerance, seven because of virologic failure, one because of another illness, one to start a clinical trial, and two out of choice. Among people continuing treatment, the week 12 viral load dropped a median 2.5 logs (range 1.3 to 5.6 logs) and the week 24 viral load 1.9 logs (range 1.3 to 5.6). Fifteen of 20 people (75 percent) assessed at week 12 had a viral load below 400 copies/mL, as did 12 of 19 (63 percent) at week 24. Six of eight people who had PI dose reductions had fewer than 400 copies/mL at week 12. The three people who started with lower PI doses had 90, 60, and fewer than 50 copies/mL at week 24.

CD4 counts climbed a median of 166 cells/mm^3 (range 25 to 448 cells/mm^3) at week 12 and 212 cells/mm^3 (range 64 to 482 cells/mm^3) at week 24. Among 13 virologic nonresponders, 11 (85 percent) gained a median 199 cells/mm^3 by week 12. The seven virologic nonresponders still taking LPV/RTV/IDV at week 24 gained a median 266 cells/mm^3 (range 50 to 248 cells/mm^3).

Jean-Luc Delassus (Ballanger Hospital Center, Aulnay sous Bois, France) opted for LPV/RTV plus 1,000 mg of SQV twice daily without reverse transcriptase inhibitors in 11 men and seven women who had tried an average of five earlier regimens (range three to nine) [abstract 7.4/12]. Their presalvage viral load averaged 37,345 copies/mL (range 7,900 to 243,000 copies/mL) and their starting CD4 count 223 cells/mm^3 (range 67 to 542 cells/mm^3).

Defining nonresponse as failure to clip at least 1 log off the viral load after 24 weeks, Delassus counted 14 responders (78 percent) and four nonresponders. The average viral load fell 1.7 logs, and 10 people (55 percent) reached a load below 50 copies/mL. CD4 counts climbed by a mean 47 cells/mm^3 (range 19 to 120 cells/mm^3). Delassus attributed the virologic failures to poor adherence resulting from side effects and pill count. The relatively good response in this study can be traced to the lack of baseline PI mutations that might compromise LPV or SQV. No mutations emerged during the 24 weeks of follow-up.

The lessons from these three small studies seem straightforward. Among people who can tolerate triple-PI therapy—and who have virus still relatively susceptible to the PIs used—virologic responses can be good despite a fat dossier of earlier treatment. Therapeutic drug monitoring may be essential with this approach to adjust overly high or low doses. Many people in all three studies had good CD4 gains, even if the new regimen failed to put the clamps on replication.

Laurenroth-Mai made the interesting observation that adding an NNRTI or TDF to triple-PI salvage adds little antiviral muscle, even in people who might be expected to respond to those drugs. Findings like that could magnify doubts about megasalvage regimens. But it would be interesting to see what such people might gain from adding ENF to the mix.

Efavirenz as only new rescue drug in children

A study of 109 children starting EFV at six Spanish centers found that the non-nucleoside worked well in all but one group—those with an earlier treatment failure [abstract F10/2]. After a median 86.5 weeks of follow-up, only 28 of 85 children in this group (33 percent) had a viral load below 400 copies/mL. But that poor response rate cannot be blamed entirely on EFV, reported E. Parada (Hospital Sant Joan de Déu, Barcelona), because in most of these 85 children EFV was the *only* new drug in the rescue regimen.

The study involved all children at the six centers who started EFV from January 2000 to June 2003. Their median age was 9.3 years (range 27 months to 17 years), and one third had AIDS. Forty-six children (44 percent) had stopped EFV after two to 214 weeks of follow-up, 33 (30 percent) because of virologic failure.

Three of five children who started antiretrovirals with an EFV regimen, six of seven who switched to EFV to simplify therapy, and six of nine who switched to EFV because of side effects of other drugs had a viral load below 400 copies/mL at the end of follow-up. Four of eight children with central nervous system side effects had to stop EFV, but none of 20 children with rash stopped the NNRTI. Cholesterol or triglycerides rose in 13 children, and 20 had diarrhea after starting EFV.

TALES OF TOXICITY

No big HIV meeting can pass without at least one slide session and several poster rows on antiretroviral toxicity. Warsaw proved no exception, though some of the news was good. Two studies outlined the advantages of swapping d4T for TDF, one documented the safety of low-dose ddI with TDF, and another suggested that lactate gains are benign and self-limited in children exposed to antiretrovirals during birth. Two bad-news reports also drew attention—and both involved cardiovascular disease.

Heart hospital admissions and more carotid lesions

Longer survival with HIV, frequent coinfection with hepatitis viruses, and hepatotoxic antiretrovirals have stoked concerns that an epidemic of liver disease threatens people with HIV more than the long-term risk of cardiovascular complications. But in one cohort of 756 people taking potent antiretrovirals, hospital admissions for heart disease already outranked those for liver disease, kidney disease, anemia, and opportunistic infections in the first half of 2000 [abstract 9.5/3]. The only more frequent admission diagnosis was nonopportunistic infection.

Carl Fichtenbaum (University of Cincinnati) sifted through a managed care database looking for everyone between 18 and 90 years old taking three or more antiretrovirals between January 1 and June 30, 2000. Among the 756 people identified, 174 checked into the hospital during that period, and total admissions numbered 340. The median age of those admitted was 46 years, 77 percent were men, and 71 percent had taken PIs. The main reasons for admission, figured per 100 patients, were:

- Nonopportunistic infections: 9.8
- Atherosclerotic cardiac or vascular disease: 8.5
- Renal disease: 5.8
- Hepatotoxicity: 5.6
- Anemia, neutropenia, or thrombocytopenia: 5.0
- Opportunistic infections: 3.4

The rate for heart disease admissions significantly exceeded the rate for hepatotoxicity ($P < 0.05$). Four of five cardiovascular admissions involved men, and the average age at admission was 55.6 years. Fichtenbaum found that 42.5 percent admitted for heart problems had hypertension and 22.5 percent had diabetes. He urged colleagues caring for people with HIV infection to pay closer attention to risk factors for cardiac, renal, and hepatic diseases.

This study did not discern whether PI therapy itself raised the risk of admission for heart disease. But just after the Warsaw meeting French researchers published their much-discussed analysis of men in the French Hospital Database on HIV.[23] PI therapy, they found, boosted the risk of myocardial infarction (MI) 2.56 times overall (95 percent confidence interval 1.03 to 6.34). Calculating standardized morbidity ratios in men using PIs compared with French men in the general population, researchers found that the ratio climbed from 0.8 for men taking PIs fewer than 18

Table 9. **New carotid lesions and plaques in people taking antiretrovirals**

n	*PI therapy* 105	*NNRTI therapy* 120	*NRTIs or no therapy* 60
Median time since HIV diagnosis (y)	8	6	6
Median time on antiretrovirals (m)	26	24	23
Acquired carotid lesions, *n* (%)	55 (52.4)	19 (15.8)	9 (15)
Total carotid plaques, *n* (%)	30 (28.6)	9 (7.5)	6 (10)

Source: Paolo Maggi, abstract 9.5/1.

months, to 1.5 for men taking PIs for 18 to 29 months, and to 2.9 for men taking PIs for 30 months or longer.

At the Warsaw conference, Paolo Maggi (University of Bari, Italy) suggested the prelude to those MIs by using color Doppler ultrasonography to chart the evolution of premature carotid vascular lesions in people taking different regimens [abstract 9.5/1].

The cohort for this ongoing study includes 105 people taking a PI regimen, 120 taking an NNRTI regimen, and 68 taking only NRTIs or no antiretrovirals. Men make up about 75 percent of each group, and the groups' median ages range from 35 to 38. Fewer people in the PI group (39 percent) than in the NNRTI group (53 percent) or the NRTI group (54 percent) have a family history of heart disease. Two thirds of the PI and NNRTI groups smoke, as do three quarters of the NRTI group. High triglycerides are more common in PI takers (44 percent) than in those on NNRTIs (27.5 percent) or NRTIs (17.6 percent).

The PI group also has the highest rate of carotid lesions and plaques (Table 9), although treatment has lasted only about two years in all three groups. Significant predictors of carotid lesions included older age ($P = 0.03$), cigarette smoking ($P = 0.02$), high triglycerides ($P = 0.017$), and PI therapy versus NNRTIs, NRTIs, or no therapy ($P = 0.011$).

TDF replacing d4T, and given with ddI

Lipids and lactates fell in 33 people with lipoatrophy who traded d4T for TDF, and the mitochondrial DNA (mtDNA) to nuclear DNA (nDNA) ratio in blood cells rose somewhat after the switch [abstract F16/4]. Esteban Ribera (Vall d'Hebron Hospitals, Barcelona) recruited 33 people with a viral load below 50 copies/mL for more than six months while taking a d4T-containing regimen. At a median CD4 count of 471 cells/mm^3, they switched d4T for TDF and continued their other drugs.

Twenty-five people have reached six months of follow-up. The only one to suffer a virologic rebound (to 1,400 copies/mL with the M184V mutation) ended up taking TDF, 3TC, and ABC, the regimen that stumbled badly in two trials[4,5] reported after Ribera started his study. Everyone else continued their new TDF regimen. The group's median CD4 count climbed to 560 cells/mm^3 by week 24, while median cholesterol fell (from 252 to 208 mg/dL, $P < 0.001$), as did triglycerides (from 366 to 216 mg/dL, $P = 0.013$). Among people who swapped d4T for TDF with a venous lactate above 2.1 mmol/L, the median value fell from 2.85 to 1.60 mmol/L.

Ribera proffered some evidence that TDF reverses the mitochondrial toxicity linked to d4T by measuring mtDNA in peripheral blood mononuclear cells with real-time PCR. The mtDNA/nDNA ratio measured 47 at the time of the switch, significantly lower than the ratio of 79 in a control group of treatment-naive people with HIV infection ($P < 0.01$). By week 12 the ratio in the TDF group improved from 47 to 69 ($P < 0.05$). But by week 24 the ratio had slipped back to 54, a non-significant change from baseline. David Cooper (University of New South Wales, Sydney) suggested that failure to find a significant 24-week improvement in the mtDNA/nDNA ratio may reflect the relatively poor sensitivity of assays measuring mtDNA in blood rather than fat.

A larger but less rigorous study catalogued changes in viral load, CD4 count, lipids, and liver enzymes in 93 people with advanced HIV infection who replaced d4T with TDF [abstract 9.8/2]. Gauging the specific effect of TDF in this tradeoff is more difficult than in Ribera's study because 44 people also changed other drugs in their regimen, usually to a non-nucleoside and ABC. Carl Knud Schewe (Practice St. Georg, Hamburg) reported that the new regimens kept CD4 counts stable, usually controlled HIV better, and generally eased toxicity markers.

At an average age of 46.1 years, the group had taken antiretrovirals for a mean 7.4 years. Sixty-six of them (71 percent) had taken a suboptimal regimen, and half had moderate to severe lipodystrophy, as judged by their clinicians. After they switched to a TDF regimen, the mean CD4 count stayed where it started—between 500 and 600 cells/mm^3—over 21 months of follow-up. The proportion of people with a viral load below 50 copies/mL rose from 60.2 percent at baseline to 77.6 percent at month six ($n = 77$, $P = 0.003$), 78.8 percent at month 12 ($n = 53$), and 80 percent at month 18 ($n = 20$). Seven people (7.5 percent) had virologic breakthroughs after dropping their d4T regimen. All of these people either had difficulty adhering to the new regimen or had taken dual-NRTI combos for more than a year.

Total cholesterol dropped significantly from the time of the switch to the last observation (231 to 202 mg/dL, $P < 0.0001$), though that drop included significant dwindling of both HDL-C (45 to 42 mg/dL, $P = 0.009$) and low-density lipoprotein cholesterol (130 to 119 mg/dL, $P < 0.001$). Gamma-glutamyl transferase, AST, and ALT all fell significantly after the switch. Creatinine inched nonsignificantly upward.

Analysis of 207 people enrolled in the US HIV Outpatient Study (HOPS) confirmed the safety of combining TDF with once-daily ddI at a dose of 250 mg or lower [abstract F16/5]. TDF boosts ddI exposure about 60 percent and so ratchets up the risk of toxicity. The 140 people who took high-dose ddI (400 mg once daily or 250 mg if weighing less than 60 kg) had more problems than the 67 taking ddI at a lower dose.

Benjamin Young (Rose Medical Center, Denver) reported that 28 percent taking high-dose ddI versus 13 percent taking low-dose ddI had any treatment-related toxicity ($P = 0.02$). People on a higher ddI dose stopped the NRTI about twice as often as those on a lower dose (20 versus 10.4 percent), but that difference fell shy of statistical significance ($P = 0.09$). New diagnoses of neuropathy (11.4 versus 2.5 percent) and pancreatitis (4.4 versus 0

Rynek Starego Miasta—the market square of Warsaw's Old Town—and the Warsaw Ghetto site offer a stark contrast in urban reconstitution.

percent) also proved more common with high-dose ddI, but again not significantly so.

High lactates and cranial sutures in kids

A study of 125 children perinatally exposed to antiretrovirals but not infected with HIV found significantly higher but steadily declining lactate levels when compared with age-matched controls for 12 months after birth [abstract F10/5]:

- Week six: 2.86 versus 1.61 mmol/L ($P < 0.0001$)
- Month three: 2.76 versus 1.49 mmol/L ($P < 0.0001$)
- Month six: 1.91 versus 1.39 mmol/L ($P < 0.0001$)
- Month 12: 1.70 versus 1.24 mmol/L ($P < 0.0001$)

Mean peak lactates drifted down from 8.06 mmol/L at week six and 10.10 mmol/L at month three to 7.28 mmol/L at month six and 4.28 mmol/L at month 12. Antoni Noguera (University of Barcelona) reported that most children had been exposed to ZDV during labor or gestation, while some had been exposed to ddI, d4T, 3TC, an NNRTI, or a PI. He noted no cases of lactic acidosis, although three girls with high lactates had mild delays in neurologic development. By eight months of age, all three were neurologically normal. In a multivariate analysis of the risk of high lactates according to NRTI exposure during gestation, only ddI raised the risk—by 1.04 per week of ddI exposure.

Follow-up of 91 children born to HIV-infected mothers documented an astonishingly high rate of a rare developmental abnormality—craniosynostosis, the premature closure of one or more cranial sutures that can result in a misshapen skull [abstract F10/1]. Whereas the incidence of this problem measures only 0.0005 percent in the general population, Dominik Dunsch (Klinik für Kinderheilkunde und Jugendmedizin, Frankfurt, Germany) found it in 18 of 91 antiretroviral-exposed children (20 percent). Head circumference in all of them was normal; the diagnoses depended on ultrasound scans and x-rays.

Four children suffered from failure to thrive and muscular hypotonia, one had episodes of convulsion and fever, and two had abnormal electroencephalograms. All of the children had been perinatally exposed to ZDV, but that finding may be coincidental because of the wide use of ZDV to prevent mother-to-child transmission of HIV. Still, all of the mothers had also taken ZDV as CBV, four with NVP and three with RTV/SQV. Maternal smoking did not correlate with diagnosis of the suture problem.

Despite the surprisingly high incidence in this case series, session cochair Carlo Giaquinto (University of Padova, Italy)

Table 10. **Dosing frequency, pill burden, adherence, and response in Hamburg**

	1997	*1999*	*2001*
n	*214*	*229*	*217*
Taking PI regimen (%)	72	40	32
Taking NNRTI regimen (%)	0	37	53
Dosing frequency (per day)	3.3	2.6	2.1
Number of tablets (per day)	13	10	6
100% adherence (pill count, %)	68	73	73
100% adherence (dosing time, %)	42	61	67
100% adherence (pills and time, %)	43	51	55
CD4 count (cells/mm^3)	260	324	425
Viral load (copies/mL)	25,000	150	25

Source: Thore Lorenzen, abstract 10.1/16.

maintained that a blinded case-control study will be needed to confirm a link between craniosynostosis and HIV infection or antiretrovirals.

GHETTO UPRISING

Only a few will be able to hold out. The remainder will die sooner or later. Their fate is decided.[24]

Those lines could be from Defoe's *Journal of the Plague Year*, or maybe from a Castro Street diary circa 1986, or this week's mail from Guatemala. But they're not. They're from the last letter of Mordecai Anielewicz, military leader of the Warsaw Ghetto uprising. Anielewicz wrote the letter on April 23, 1943, a little more than 60 years before the 9th EAC. After the city's demolition in World War II, Varsavians lovingly restored their Old Town, brick by brick, providing quaint distraction for some conference attendees with time to spare. The Ghetto, only three or four blocks to the west, was not restored after the Germans leveled it in 1944. Communist-era concrete flats now mark the spot, along with a bare park bounded on one side by Anelewicza Street. At the park's eastern end stands a monument to Anielewicz and his motley band.

The story of the uprising is brief and bloody.[25] The Nazis created the Ghetto, shut it off with a 10-foot wall, and began secluding Warsaw's half-million Jews there in 1940. Some found no housing, others lived 13 to a room. They started dying of starvation and typhoid. On July 22, 1942, Germans began herding residents to the train station outside the Ghetto's west wall. At the tracks' other end lay Treblinka.

To encourage cooperation, the Nazis told the Jews they were going to Arcadian labor camps. But a few Jews who escaped the Ghetto had learned the truth. When word came back to Warsaw, residents formed the Yidishe-Kamf-Organizatsie (Jewish Fighting Organization), Zydowska Organizacja Bojowa in Polish. They had one pistol among them. But when the Nazis came to round up more Jews on January 18, 1944, the resistance had more guns, and they drove the Nazis out. Deportations stopped after that until April 19, when the Nazis assaulted the Ghetto with tanks, rapid-fire artillery, and flamethrowers. The resistance held out for one month, during which the Nazis killed or deported 56,000 Jews. Some of the Jews, including Anielewicz, killed themselves.

This story of bravery against impossible odds—one pistol versus the SS—underlines a verity often forgotten by the secure and powerful: People facing certain death can be alarmingly feisty. One can cite proofs of this theorem stretching from the histories of Josephus to yesterday's Johannesburg *Times*.

When gay men and hemophiliacs in the United States discovered they were dying of an incurable infection, they forced the government to fund research, changed the way the FDA approves drugs, revamped the format of scientific meetings, and demanded equal footing with the physicians treating them and the scientists studying their disease.[26] When South Africans with AIDS learned that drugs were saving lives of their counterparts in Europe, North America, and Brazil, they rattled an intransigent government with protests, lawsuits, conferences, and one highly publicized abstention from treatment until the administration rethought its position on pathogenesis and agreed to launch a national treatment program.

Only a few years ago, many judged global treatment of HIV infection as far-fetched as resisting the SS. But today, Joep Lange reminded attendees in Warsaw, governments across Africa, the Caribbean, and Asia are finding ways to solve structural problems and buy enough generics to begin treating the people who need them most. Three reports at the Warsaw meeting—all of them success stories—showed what's at stake.

Thore Lorenzen (Institute for Interdisciplinary Infectious Diseases, Hamburg) has been keeping tabs on CD4 counts, viral loads, regimen type, dosing frequency, number of pills, and adherence in 660 people with HIV since 1997 [abstract 10.1/16]. In simple tables and graphs, Lorenzen told a story many HIV clinicians would recognize if they had done the same math: As people shifted from PIs to NNRTIs and regimens became simpler and more tolerable, adherence rose along with CD4 counts, while viral loads fell (Table 10). Age, gender, HIV status, and employment did not influence adherence.

At Huddinge University Hospital in Stockholm, PehrOlov Pehrson and colleagues showed what potent antiretroviral therapy can do in a mixed population of European and non-European men and women who picked up HIV sexually or from sharing needles [abstract 10.1/12]. After a median of 62 months taking at least a three-drug regimen (interquartile range 37 to 75 months), 86 percent of 410 people have a viral load under 50 copies/mL. Another 5 percent have a viral load below 500 copies/mL, and another 5 percent under 5,000 copies/mL. Among 509 people ever treated with three or more drugs, 82 percent have a viral load below the 50-copy mark, another 6 percent under 500 copies/mL, and another 5 percent under 5,000 copies/mL. Only four people (3 percent) have both a viral load above 50 copies/mL and a CD4 count under 200 cells/mm^3.

Results are equivalent in people who began antiretrovirals with three or more drugs (83 percent below 50 copies/mL) and those who started with only one or two drugs (87 percent below 50 copies/mL). European women have the best overall

response, with 96 percent under the 50-copy line. Yet 84 percent of non-European women are responders by this criterion, as are 87 percent of non-European men who acquired HIV through sex with women. Among gay and bisexual men, 90 percent have fewer than 50 copies/mL. The 50-copy response rates are lower, but still good, among injecting drug-using men (78 percent) and women (71 percent). Length of infection and pretreatment CDC disease stage had little impact on virologic response.

Why are five-year response rates in this outpatient clinic as good as—or better than—48-week results in clinical trials? Pehrson has a suggestion: "Empowerment of the patient and the staff through continuous education to induce a common view, a prolonged motivation process involving different team members, integrated clinical research and confidence building lead to increased adherence. This limits the risk of virological failure and thereby development of resistance, immunological and clinical failure."

In countries where people are just getting their first taste of antiretrovirals, evidence that they respond as well as those in a Stockholm clinic has become so routine that it hardly bears repeating. But antiretrovirals have come so slowly to these lands, and the road to full access stretches to such a distant vanishing point, that some repetition may be excused. Especially when it comes from Maun, a dusty corner of Botswana due north of the Kalahari Desert, due east of the Makgadikgadi Salt Plains, and 500 kilometers from the nearest referral hospital in Francistown. At a district hospital there, T.K. Mudiayi reported in Warsaw, 164 people with HIV have started HAART [abstract LBF11/1].

The Maun clinic is part of Botswana's national antiretroviral rollout, which aims to treat all children younger than one year old, all children older than one with a low CD4 count or AIDS, and all adults with a CD4 count under 200 cells/mm^3 or AIDS. People do not have to pay for their antiretrovirals.

Of the 164 people who started antiretrovirals in Maun (usually with NVP or EFV), eight had to stop because of advanced HIV infection and other illnesses, 36 died, and 120 have had nine to 12 months of treatment. Among 107 who had recent viral load assays, five of six children and 89 of 101 adults had a viral load below 400 copies/mL, for an 88 percent on-treatment response rate. In children the mean CD4 count climbed from 558 cells/mm^3 (range 6 to 1,324 cells/mm^3) before treatment to 784 cells/mm^3 (range 305 to 1,710 cells/mm^3) after nine to 12 months. In treatment-naive and experienced adults, baseline counts of 98 and 141 cells/mm^3 (ranges 2 to 508 cells/mm^3 and 15 to 246 cells/mm^3) rose to 256 and 276 cells/mm^3 (ranges 23 to 898 cells/mm^3 and 60 to 660 cells/mm^3).

Among the 36 deaths, nine died within one month of starting antiretrovirals and another 18 within three months, numbers showing that these people already had gravely advanced disease when antiretrovirals reached Maun. Of those who died, 25 had anemia, 15 dehydration and malnutrition, eight meningitis, and six tuberculosis. In Europe, North America, and many other places, these complications could have been managed—or would never have arisen—and the overall response to first-line therapy would have been accordingly higher.

That obvious conclusion prompted some attendees to ask Mudiayi if it wouldn't make more sense to treat more people with less advanced disease. But knowing that still-scarce antiretrovirals can rescue many with advanced disease, who would play Solomon in Maun?

In May 1943 SS Major General Jürgen Stroop blew up Warsaw's Great Synagogue and reported, "The Warsaw Ghetto is no more." Today, the walls of the world's AIDS Ghettos are crumbling—slowly, slowly. ■

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

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ABSTRACTS

New England Journal of Medicine

Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection

Robbins GK et al.

BACKGROUND: The optimal sequencing of antiretroviral regimens for the treatment of infection with human immunodeficiency virus type 1 (HIV-1) is unknown. We compared several different antiretroviral treatment strategies. *METHODS:* This multicenter, randomized, partially double-blind trial used a factorial design to compare pairs of sequential three-drug regimens, starting with a regimen including zidovudine and lamivudine or a regimen including didanosine and stavudine in combination with either nelfinavir or efavirenz. The primary end point was the length of time to the failure of the second three-drug regimen. *RESULTS:* A total of 620 subjects who had not previously received antiretroviral therapy were followed for a median of 2.3 years. Starting with a three-drug regimen containing efavirenz combined with zidovudine and lamivudine (but not efavirenz combined with didanosine and stavudine) appeared to delay the failure of the second regimen, as compared with starting with a regimen containing nelfinavir (hazard ratio for failure of the second regimen, 0.71; 95 percent confidence interval, 0.48 to 1.06), as well as to delay the second virologic failure (hazard ratio, 0.56; 95 percent confidence interval, 0.29 to 1.09), and significantly delayed the failure of the first regimen (hazard ratio, 0.39) and the first virologic failure (hazard ratio, 0.34). Starting with zidovudine and lamivudine combined with efavirenz (but not zidovudine and lamivudine combined with nelfinavir) appeared to delay the failure of the second regimen, as compared with starting with didanosine and stavudine (hazard ratio, 0.68), and significantly delayed both the first and the second virologic failures (hazard ratio for the first virologic failure, 0.39; hazard ratio for the second virologic failure, 0.47), as well as the failure of the first regimen (hazard ratio, 0.35). The initial use of zidovudine, lamivudine, and efavirenz resulted in a shorter time to viral suppression. *CONCLUSIONS:* The efficacy of antiretroviral drugs depends on how they are combined. The combination of zidovudine, lamivudine, and efavirenz is superior to the other antiretroviral regimens used as initial therapy in this study.

NEJM 2003;349(24):2293-2303.

Journal of Antimicrobial Chemotherapy

Long-term virological outcome and resistance mutations at virological rebound in HIV-infected adults on protease inhibitor-sparing highly active antiretroviral therapy

De La Rosa R et al.

OBJECTIVE: To assess the durability of the undetectability of HIV plasma viremia (pV) and to determine the factors associated with virological rebound (VR) in HIV-infected adults on protease inhibitor (PI)-sparing highly active antiretroviral therapy (HAART). The development of resistance mutations during virologically successful therapy and VR was also analyzed. *MATERIALS AND METHODS:* One hundred and twenty-six HIV-infected adults on PI-sparing HAART were prospectively followed from April 1998 to December 2002: Group 1, naive for antiretroviral drugs (n = 26); Group 2, previously PI-HAART-exposed patients (n = 19); Group 3, previously exposed to suboptimal therapy (n = 81). Genotypic resistance tests on peripheral blood mononuclear cells or on plasma RNA (when feasible) were carried out when undetectable HIV pV was demonstrated for at least 48 weeks. Additionally, patients showing a therapy adherence >95 percent developing VR were also tested at rebound, at simplification and during previous suboptimal therapy exposure. *RESULTS:* The median follow-up time was 630 [329-903] days. VR was considered as two consecutive pV levels >50 copies/mL. Twenty-two (17.5 percent) patients developed VR. Only therapy adherence <95 percent was independently associated with VR (adjusted hazard ratio: 8.42; 95 percent CI: 3.33-21.27). Twenty (40 percent) of the 50 patients with pV <50 copies/mL for at least 48 weeks showed at least one thymidine-associated mutation (TAM) but none had NNRTI-resistance mutations. Ten (83.3 percent) of 12 available adherent patients showing VR harbored NNRTI-resistance-associated mutations; 50 percent of them were considered as wild-type strains at simplification time. However, the TAM number and resistance mutations profile found on suboptimal exposure were very similar to those found at VR on simplification therapy. *CONCLUSIONS:* PI-sparing HAART allows maintenance of successful long-term control of HIV replication, adherence to therapy being the main factor associated with VR. However, a small proportion of patients on simplification regimen may develop VR regardless of therapy compliance. VR on PI-sparing HAART is characterized by the emergence of NNRTI cross-resistance mutations. Finally, TAMs "archived" during previous suboptimal exposures are partially involved in subsequent VR on simplification HAART.

J Antimicrob Chemother 2004;53:95-101.

Journal of Hepatology

Dynamics of plasma hepatitis B virus levels after highly active antiretroviral therapy in patients with HIV infection

Fang CT et al.

BACKGROUND: The optimal strategy to prescribe highly active antiretroviral therapy (HAART) in patients infected with both hepatitis B virus (HBV) and human immunodeficiency virus (HIV) remains unsettled. This study aimed to compare the HBV dynamics between HBeAg-positive and HBeAg-negative coinfected patients treated with lamivudine-containing HAART. *METHODS:* We retrospectively analyzed the serial changes of plasma HBV DNA levels in 24 HBsAg-positive HIV-infected patients who entered the HAART program. A polymerase chain reaction-based assay, capable of quantifying as few as 400 HBV copies/ml, was used. The median follow-up time was 18 months. *RESULTS:* HAART containing lamivudine 300 mg/day effectively suppressed plasma HBV-DNA to 10(-3)-10(-5)-fold of the baseline levels, but a multi-phasic decay of HBV DNA was observed. The later phases became flat, as a persistent residual HBV viremia, in eight of the studied 10 HBeAg-positive patients; in contrast, residual HBV viremia was not observed in the 10 HBeAg-negative patients studied (8/10 vs 0/10, P = 0.0007, Fisher's exact test). HAART without lamivudine did not suppress plasma HBV DNA levels in the remaining four patients. *CONCLUSIONS:* HAART containing lamivudine 300 mg/day effectively suppresses HBV replication in HBeAg-negative HIV/HBV-coinfected patients. Nevertheless, residual HBV replication persisted in most HBeAg-positive coinfected patients.

J Hepatol 2003;39(6):1028-35.

Journal of Acquired Immune Deficiency Syndromes

Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort

O'Brien ME et al.

OBJECTIVES: To describe the patterns and correlates of discontinuation of the initial highly active antiretroviral therapy (HAART) regimen in an urban, outpatient cohort of antiretroviral-naive patients. *DESIGN:* Retrospective cohort of 345 randomly selected antiretroviral-naive patients who initiated HAART on six selected regimens between January 1997 and May 2001 in New Orleans. *METHODS:* An investigator reviewed medical records to collect information on concurrent medications, symptoms/diagnoses, staging indicators, and reasons for HAART discontinuation. Proportional hazards regression methods were used to identify predictors of discontinuation. *RESULTS:* After a median follow-up of 8.1 months, 61 percent of patients changed or discontinued their initial HAART regimen; 24 percent did so because of an adverse event. The events most commonly cited as the cause for discontinuation were nausea, vomiting, and diarrhea. A detectable viral load was associated with discontinuation at any time, while reporting nausea/vomiting or dizziness at the previous visit were associated with discontinuation during the first three months on HAART. Nausea/vomiting and not having AIDS at the time of HAART initiation were associated with discontinuation due to an adverse event at any time, while a high viral load, and dizziness or anorexia/weight loss at the previous visit were associated with discontinuation due to an adverse event in the first three months on HAART. *CONCLUSIONS:* Gastrointestinal adverse events of HAART are the most frequently cited reason for discontinuation of HAART. An effort should be made to educate patients about these events and to encourage continued adherence. Additionally, appropriate prophylaxes for these events are warranted.

J Acquir Immune Defic Syndr 2003;34(4):407-14.

Treating HCV infection in HIV/HCV-coinfected patients

Brian Boyle

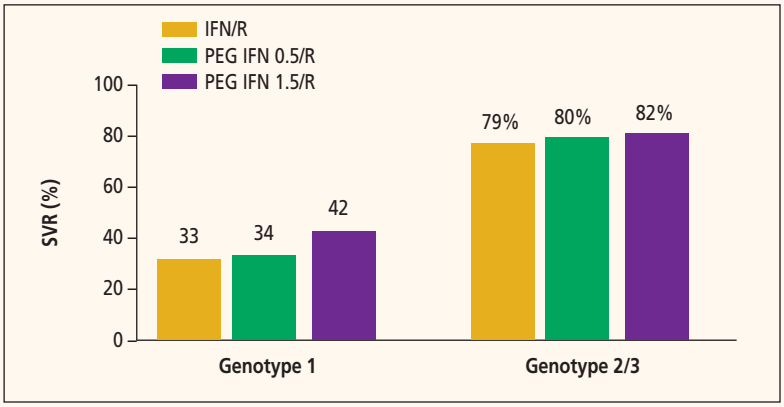
Hepatitis C virus (HCV) was initially identified in 1989 when it was found to be the primary causative agent of non-A, non-B hepatitis, a condition associated with high rates of progressive liver disease, cirrhosis, end-stage liver disease, and hepatocellular carcinoma.

Since being identified, appreciation of the significant worldwide health impact of chronic HCV infection has grown. Approximately 170 million people, or 3 percent of the world's population, are infected with HCV, and the annual toll in lives and lost productivity due to HCV is staggering. In the United States alone, approximately 4 million people, or 1.8 percent of the population, are infected, and 10,000 people die each year due to HCV-related complications.

HCV is an enveloped RNA virus in the flaviviridae family, which has 10 variants, referred to as genotypes. The HCV genotype with which the person is infected is important, since it is somewhat predictive of the likelihood of HCV disease progression[1] and highly predictive of the likelihood of treatment success. It is now well established that genotypes 1 and 4 have the lowest rates of treatment success, while genotypes 2 and 3 have the highest.

The prevalence of HCV infection and of various HCV genotypes has significant geographic variability. HCV infection rates are approximately 1 percent to 2 percent in the United States and Europe, while some countries in South America, Africa, and Asia have rates from 2.5 percent to 10 percent. Further, while in many areas of the world—for example, Europe—genotypes other than 1 may predominate, in the United States genotype 1 is the most common, with genotypes 1, 2, 3 and 4 infecting approximately 71 percent, 14 percent, 12 percent, and 2 percent, respectively, of HCV-infected patients, while cumulatively genotypes 5 to 10 infect <1 percent of those patients.[2] Due to the high prevalence of HCV genotype 1 in the United States, achieving high rates of treatment success, especially in HIV/HCV-coinfected patients, can be challenging.

Figure 1. **NIH consensus HCV evaluation and treatment algorithm[3]**



Patients infected with HCV have an 80 percent to 85 percent chance that the HCV infection will persist and that they will go on to have a chronic HCV infection. Chronic HCV infection has multiple manifestations, the most common of which is chronic, progressive liver disease associated with inflammation and fibrosis that in some patients may progress to cirrhosis. Cirrhosis, or end-stage liver disease, is associated with multiple complications including variceal bleeding, ascites, encephalopathy, and hepatocellular carcinoma. These conditions are common causes of morbidity and mortality in HCV-infected patients. In addition to liver disease, HCV-infected patients are also at risk for other "extrahepatic" medical conditions, including essential mixed cryoglobulinemia, Sjögren's syndrome, lichen planus, renal disease, arthritis, and porphyria cutanea tarda.

The evaluation and treatment of HCV infection are complex. An algorithm from the 2002 NIH Consensus Development Conference on the management of HCV provides a useful and simple algorithm for the diagnosis and treatment of HCV in HCV-mono-infected patients. (Figure 1)

As discussed below, the NIH consensus algorithm is not necessarily applicable in all respects to HIV/HCV-coinfected patients.

HIV/HCV coinfection

Due to shared risk factors, HCV infection is present in a higher percentage of HIV-infected patients than the population as a whole. It is estimated that 300,000 people in the United States are HIV/HCV-coinfected, and, in some studies of HIV-infected, urban populations, HCV coinfection was found in 40 percent of all patients and 90 percent of persons who had hemophilia or a history of intravenous drug use (IDU). (Figure 2)

While most HIV/HCV-coinfected patients have intravenous drug use as a risk factor for HCV, other risk factors, including bloody fights, tattoos, body piercing, and unprotected anal or vaginal sex, also may have been the cause of HCV infection.[5-7] There is even some evidence for salivary shedding of HCV, which allows for the possibility that oral contact is another method for non-parenteral transmission of HCV.[8]

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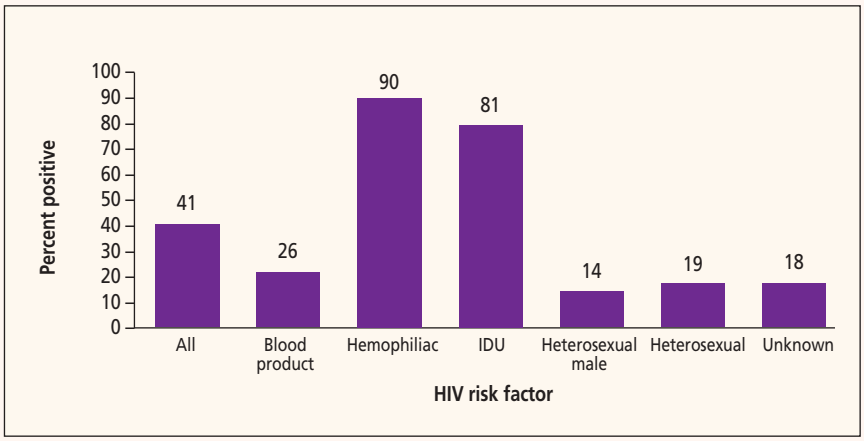
Figure 2. **HCV seroprevalence by HIV risk factor[4]**



Since highly active antiretroviral therapy (HAART) became widely available in 1996, morbidity and mortality related to HIV infection have remarkably declined.[9] In the meantime, however, the proportion of patients suffering morbidity or mortality related to liver disease, much of it related to chronic HCV, has risen significantly.[10] The cause of this increased morbidity and mortality is likely to be multifactorial. Studies have demonstrated that HIV/HCV-coinfected patients may be at particularly high risk for cirrhosis and end-stage liver disease, hepatocellular carcinoma, and extrahepatic manifestations of HCV.[11,12] Factors that may contribute to these higher rates of HCV-related complications in HIV/HCV-coinfected patients include:

- Higher baseline HCV viral loads;
- Continued alcohol use/abuse;
- Immunocompromising conditions, especially a CD4 count <200 cells/mm^3; and
- Liver toxicity from certain antiretroviral therapies (eg, high-dose ritonavir [RTV] and nevirapine [NVP]).

Further, while controversial, some studies have also shown that HIV/HCV-coinfected patients may experience more rapid progression of their HIV infection and have compromised immune reconstitution with HAART compared to HIV-mono-infected patients.[13-16]

HCV evaluation in HIV/HCV-coinfected patients

The first step in providing appropriate monitoring and therapy for HIV/HCV-coinfected patients is to identify them. The recommendations of 1999 USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections provide that all patients infected with HIV should be tested for HCV, and that HCV-positive patients should be counseled regarding their need for evaluation and, if appropriate, treatment of HCV.

Like HCV-mono-infected patients, the evaluation of an HIV-infected patient should include HCV serology; however, given the possibility of a false negative HCV serology in HIV-infected patients,[17] consideration should be given to confirming a negative HCV serology by checking a qualitative HCV RNA PCR for the presence of HCV. In addition, HIV/HCV-coinfected patients should be counseled to avoid alcohol use and, if not immune, should be vaccinated against infection with hepatitis A or B virus.[18]

Since transaminitis, HCV viral load or genotype, and liver imaging—for example, liver ultrasound or computerized tomography—do not always correlate with the degree of HCV-related liver inflammation or fibrosis, a liver biopsy is indicated in most HIV/HCV-coinfected patients. A liver biopsy is associated with some risk—complication rates, mainly bleeding, are generally in the 1 percent to 3 percent range and the risk of mortality is <.01 percent—but the biopsy is important not only to establish the patient's current level of liver disease but also to predict the patient's risk of progression to cirrhosis, which is one indicator of the need for prompt treatment, and to rule out other liver diseases that may impact the patient's HCV treatment (eg, non-alcoholic steatohepatitis).

There are a number of methods for assessing the histologic findings of the liver biopsy. Under one commonly used system, the METAVIR histologic scoring system, inflammation is graded from 0 (none) to 3 (severe) and fibrosis is staged from 0 (no fibrosis) to 4 (cirrhosis).

HCV-mono-infected patients with mild fibrosis (portal fibrosis without septa; stage 1) have a low risk of progression to cirrhosis over 15 years, while patients with more advanced fibrosis, indicated by stages 2 (portal fibrosis with few septa) and 3 (portal fibrosis with many septa), are at increased risk with a median time to progression to cirrhosis of 10 years and 18 months, respectively.

While a biopsy is generally desirable, treatment without biopsy may be reasonable in patients who are newly or recently infected with HCV or are infected with HCV genotypes 2 or 3 and those patients without stigmata of advanced HCV who refuse biopsy but are willing to accept HCV therapy.

HIV and HCV treatment

Decisions regarding if and when to treat HIV/HCV-coinfected patients for their HCV disease requires close collaboration between the physician and the patient. This decision should include an assessment of the risks to the patient of HIV or HCV disease progression, the patient's risk of adverse consequences of HIV or HCV treatment, the likelihood that the patient will be able to take and tolerate HCV therapy—for example, issues surrounding continuing psychiatric disease, intravenous drug use or alcohol abuse should be addressed, if at all possible, prior to therapy being started—and the chance for a positive effect from the treatment, including slowing or reversion of fibrosis, prevention of HCV-related complications, and/or a sustained virologic response (SVR).

It is extremely important that clinicians keep in mind that while for some patients—for example, those with early HCV disease, HCV genotypes 2 or 3, and a CD4 count >200 cells/mm^3—the goal of HCV treatment is usually viral eradication, in other patients—for example, those with more advanced HCV disease, HCV genotypes 1 or 4, and a CD4 count <200 cells/mm^3—the goal may be to decrease ALT and HCV RNA, decrease fibrosis progression, decrease the risk of hepatoma and decrease the risk of death, all of which HCV treatment can achieve, even in the absence of achieving a virologic cure.

Balancing all the factors involved in making the decision to immediately treat HCV or defer therapy is often complex and requires a case-by-case approach. In making these decisions, clinicians and patients should be guided by information regarding the predictors of successful HCV therapy, which include:

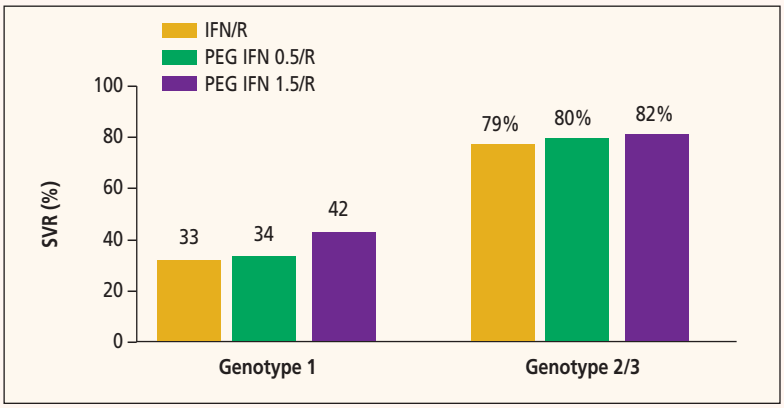
- non-1 HCV genotype;
- no or low levels of fibrosis on liver biopsy;
- higher baseline CD4 count;
- lower HCV viral load (<2 million copies/mL);
- younger age (<40 years); and
- female gender.

The clinician and patient should also consider the absolute or relative contraindications to HCV treatment:

- decompensated liver disease;
- active alcohol or drug use (controversial);
- severe depression or other psychiatric disease;
- significant blood count abnormalities;
- autoimmune disorders;
- pregnancy;
- cardiovascular disease;
- diabetes mellitus; and
- renal failure.

While deferral of therapy is not unusual in clinically stable patients with stage 0-1 fibrosis, especially those with HCV genotype 1 (due to lower chance of SVR), clinicians and patients who opt to defer therapy should keep in mind that progression to cirrhosis in HIV/HCV-coinfected patients may be significantly more rapid than in HCV-mono-infected patients. Therefore, if treatment is deferred, a follow-up biopsy should be performed approximately every three years (the exact timing is controversial) to reassess and monitor the patient's status. Further, clinicians and patients should be mindful of data that indicate that early treatment in patients with mild fibrosis is cost effective and resulted in improved outcomes.[19,20]

Figure 3. **Sustained virologic response by genotype[24]**



Prior to deciding to defer HCV treatment, however, clinicians and patients should consider whether the best opportunity for HCV treatment may be missed. Unlike HCV-mono-infected patients, who generally experience slow progression of HCV-related liver disease and maintain a relatively intact immune system throughout their lifetime, the window of opportunity to treat HCV infection in HIV/HCV-coinfected patient's may be significantly smaller.

First, it is clear that the more intact the patient's immune system—in particular, having a CD4 count >200 cells/mm^3—the higher the likelihood of significant response or sustained virologic response to the HCV therapy. Therefore, if the HCV therapy is delayed too long, the chance for successful therapy may be compromised.

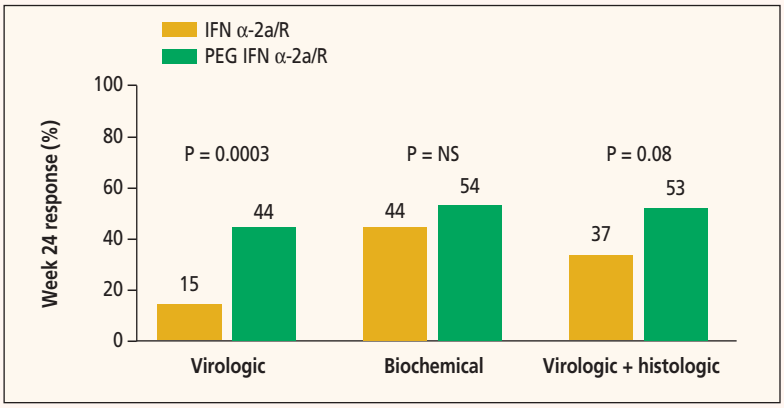
Second, since adherence to HCV therapy is critical for success, having the patient on as few medications as possible—and only the HCV therapy, if possible—is obviously desirable in order to minimize the chance of treatment fatigue, additive side effects, or drug interactions. This line of logic would support starting therapy at an early juncture, preferably prior to the need for HAART, but to this point studies have not definitively established this approach. An AIDS Clinical Trial Group (ACTG) study will shed some light on this issue by evaluating in HIV/HCV-coinfected patients with CD4 counts >350 cells/mm^3 whether it is better to start HAART (for six months) and then add HCV therapy or treat HCV first, and add HAART later.

Of course, it should be noted that if HAART is used in combination with HCV therapy, and ribavirin in particular, caution should be exercised regarding the use of didanosine (ddI) (increased intracellular levels increase risk of toxicity), zidovudine (ZDV) (risk of additive anemia due to bone marrow suppression and decreased ZDV efficacy due to decreased phosphorylation), and stavudine (d4T) (risk of decreased efficacy due to decreased phosphorylation).

Finally, the decision about whether to treat HIV or HCV first, or treat both simultaneously, is a complex one. This decision involves many factors that must be weighed by the clinician and the patient, including:

- the risk for HIV progression in the absence of HAART—especially since the patient's CD4 counts may be lowered by HCV therapy;
- the risk of HCV progression in the absence of treatment;

Figure 4. **ACTG 5071: Week 24 responses[26]**



- the possibility that HIV therapy—by boosting the patient's CD4 count and other potential immune benefits—can improve the chance for successful HCV therapy or the patient's degree of liver fibrosis;[21] and
- the possibility or reality of patient intolerability of HIV therapy due to hepatotoxicity.[22,23]

Needless to say, consulting a clinician experienced in making these decisions can be of great help in arriving at the appropriate treatment decision.

Preferred therapies for HCV

In the past few years, significant advances have been made in the treatment of HCV. These advances include the use of ribavirin in combination with interferon and the development of two pegylated interferons: pegylated interferon alfa-2b and pegylated interferon alfa-2a. These developments have revolutionized the treatment of HCV and are rapidly becoming the standard of care.

The combination of pegylated interferon plus ribavirin has significantly increased the percentage of patients achieving an SVR—that is, an undetectable HCV RNA level six months following the completion of therapy. These improved success rates are reflected in several studies involving HCV mono-infected patients in which treatment with pegylated interferon plus ribavirin was compared to treatment with standard interferon plus ribavirin.

In a large study by Manns *et al*, high-dose pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) achieved an overall SVR of 54 percent, with 42 percent of genotype 1 and 82 percent of genotypes 2/3 achieving SVR. In patients overall and with genotype 1, but not with genotypes 2/3, the SVR rates achieved with high-dose pegylated interferon alfa-2b plus ribavirin were significantly better than those achieved with lower doses of pegylated interferon alfa-2b (0.5 µg/kg/week) plus ribavirin (1,000-1,200 mg/day) or interferon alfa-2b (3 MU subcutaneously three times per week) plus ribavirin (1,000-1,200 mg/day).[24] (Figure 3)

In a major study by Fried *et al*, the investigators compared pegylated interferon alfa-2a (180 µg/week) alone to pegylated interferon alfa-2a (180 µg/week) plus ribavirin (1,000-1,200 mg/day) to standard interferon alfa-2b (3 MIU subcutaneously three times per week) plus ribavirin (1,000-1,200 mg/day). Overall, SVR was achieved in 30 percent, 56 percent, and 45 percent of subjects, respectively. Further, unlike the Manns study which involved pegylated interferon alfa-2b, in this trial SVR in the pegylated interferon alfa-2a plus ribavirin arm was not only significantly higher overall and in the genotype 1-infected subjects, but also was significantly higher in those subjects infected with genotypes 2/3.[25]

Preliminary results from the largest two studies conducted to date evaluating pegylated interferon and ribavirin treatment in HIV/HCV-coinfected patients—ACTG 5071 and RIBAVIC—indicate it also leads to higher rates of success in that population, especially in patients with the more difficult-to-treat HCV genotype 1. It should be noted, however, that the rates of success seen in those trials were lower than those seen in the HCV-mono-infected patients, indicating that the presence of HIV infection compromises the efficacy of HCV treatment even in patients with relatively high CD4 counts.

ACTG 5071 enrolled HIV/HCV-coinfected patients, the majority of whom were on HAART, and randomized them to pegylated interferon alfa-2a (180 µg/week) plus ribavirin (600-1,000mg/day) or interferon alfa-2a (6 MIU thrice weekly for 12 weeks followed by 3 MIU thrice weekly) plus ribavirin (600-1,000mg/day). At 24 weeks of therapy, the pegylated interferon arm achieved higher rates of virologic response overall (44 percent versus 15 percent, $p=0.0003$) and in genotype 1 patients (33 percent versus 7 percent, $p=0.0014$), and there was also a strong trend toward higher response rates in genotype 2/3 patients (80 percent versus 40 percent, $p=0.06$). (Figure 4) Predictors of virologic success included use of pegylated interferon, white race, a Karnofsky performance status of 100, and a fibrosis score of 0-2 (out of 6). Toxicities were somewhat higher in the pegylated interferon arm, in particular those patients experienced more grade 4 toxicities (11 percent versus 6 percent, $p=0.0012$) and a greater loss of CD4 cells (194 versus 112 cells/mm^3, $p=0.01$).

The RIBAVIC trial also enrolled HIV/HCV-coinfected patients, 80 percent of whom were on HAART and who had a mean CD4 count of 515 cells/mm^3, and randomized them to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or interferon alfa-2b (3 MIU thrice weekly) plus ribavirin (800 mg/day). At 48 weeks of therapy, using either an intent-to-treat or as-treated analysis, the pegylated interferon arm achieved higher rates of virologic success overall (38 percent versus 24 percent, $p=0.01$; and 51 percent versus 31 percent, $p<0.01$, respectively). (Figure 5) While rates of success were higher in patients with HCV genotypes 1 and 4, they were similar in HCV genotypes 2 and 3. Due to high rates of toxicity, over 50 percent of

Figure 5. **RIBAVIC: 48-week virologic response** [27]

Safety and tolerability: No difference in AEs between PEG IFN and IFN arms

	PEG IFN/rbv	*IFN rbv*	*p-value*
ITT analysis	59/157 (38%)	39/162 (24%)	0.01
Per-protocol analysis	50/100 (51%)	32/105 (31%)	<0.01

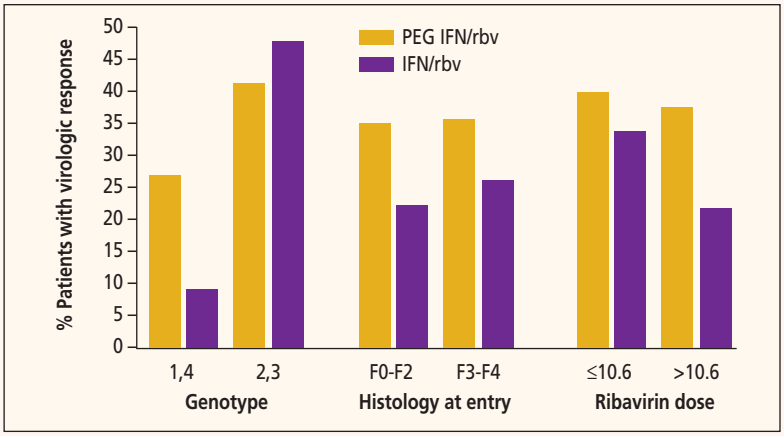


Figure 6. **Adverse events/side effects of HCV therapy** [30]

PEG-IFN	*Ribavirin*
• Neuropsychiatric	• Cough and dyspnea
– Depression (3-44%), anxiety, irritability, fatigue	• Hemolytic anemia
• Bone marrow suppression	• Teratogenicity
– Neutropenia, thrombocytopenia	• Insomnia
• Anorexia/weight loss	• Rash
• Alopecia	• Pruritus
• Exacerbation of autoimmune disorders	• Nausea
• Retinopathy	
– Cotton wool spots, thrombosis	
• Thyroid dysfunction	
– Hashimoto's thyroiditis	

the patients had discontinued therapy by week 48. The side effects and toxicities leading to these discontinuations included generalized flu-like symptoms, and gastrointestinal, psychiatric, respiratory, and dermatologic problems.

The ACTG 5071 and RIBAVIC studies indicate that response rates in HIV/HCV-coinfected patients are improved by but remain suboptimal with the use of pegylated interferon and ribavirin combination therapy. This therapy presents many unique challenges in HIV/HCV-coinfected patients, including problems with tolerance and potential non-adherence. Guidance regarding the chance of therapy success may help to encourage patient tolerance of some side effects, improve adherence and, in patients who are experiencing problems with the therapy, provide an additional basis for considering continuation of therapy.

In a recent study, HCV-mono-infected patients who failed to achieve a 2 $\log_{10}$ copies/mL decline or undetectable HCV RNA by week 12 had only a 3 percent chance of achieving SVR, while patients who did achieve that level of HCV RNA suppression had a 65 percent chance of SVR.[26] This finding has been tentatively confirmed in HIV/HCV-coinfected patients, but more data are needed before a decision is made based upon this criterion in co-infected patients.[28] Further, prior to using this criterion to discontinue HCV therapy, clinicians should consider other benefits that may accrue with that therapy (eg, a reversion of fibrosis), and whether that should also be considered an independent treatment goal.

Finally, clinicians should note that in addition to the benefits of pegylated interferon in the treatment of HCV infection, this therapy has also been shown to be effective at decreasing HIV viral loads, in some studies by as much as 0.5 $\log_{10}$ copies/mL.[29]

Management of HCV therapy side effects and toxicities

The side effects and potential toxicities of interferon and ribavirin therapy are legion. (Figure 6)

Since these discourage and prevent many patients from even starting HCV therapy, appropriate pre-therapy counseling and preparation are essential components of HCV treatment. In addition, patients should be carefully monitored while on therapy for side effects or complications that may challenge adherence to HCV treatment or place the patient at risk for morbidity or mortality. Notable considerations in this regard include:

- preparing the patient for the flu-like symptoms and local site reactions that commonly occur with interferon therapy;
- screening patients for psychiatric disease, in particular depression, prior to starting interferon and considering the use of an antidepressant prior to the initiation of HCV therapy;
- avoiding the use of medications that may increase the risk of side effects or toxicities (eg, ddI due to its established interaction with ribavirin); and
- screening patients before starting medications that may be absolutely or relatively contraindicated (eg, pregnancy and cardiovascular disease, respectively, with ribavirin).

Further, the appropriate use of medications to manage side effects (eg, acetaminophen for flu-like symptoms, and antidepressants for depression) and toxicities (eg, granulocyte-colony stimulating factor [G-CSF] for neutropenia, and erythropoietin for anemia) is likely to lead to improved adherence to and persistence with therapy.[31-35]

Conclusion

While HCV treatment is difficult for clinicians and patients, it may result in a significant improvement in the health of HIV/HCV-coinfected patients. Clinicians treating HIV-infected patients should test their patients for HCV and should aggressively pursue the evaluation and, if appropriate, the treatment of that condition. Improved outcomes and responses to therapy are likely to result from providing patients with the medical, educational, and psychosocial support needed to get them on, and keep them on, HCV therapy. ■

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ARV Update

Continued from page 9

FDA approves SQV/r

The US Food and Drug Administration (FDA) approved on December 24, 2003, new dosing regimens for the two available formulations of saquinavir (SQV)—Invirase (SQV hard-gel capsules) and Fortovase (SQV soft-gel capsules). The newly approved dosing regimen for both SQV formulations is 1,000 mg twice daily co-administered with ritonavir (RTV) 100 mg twice daily.

For Invirase, the new, RTV-boosted regimen replaces the previously approved regimen. For Fortovase, the RTV-boosted regimen allows a reduced pill burden and ease of administration compared to the previously approved regimen. However, unboosted Fortovase remains a dosage option for patients who are unable to tolerate RTV.

FDA approval of Roche Laboratories' supplemental New Drug Application (sNDA) for Invirase was based on data which showed that the hard-gel formulation of SQV 1,000 mg with RTV 100 mg twice daily provides similar to or greater levels of SQV over a 24-hour period than those achieved with the soft-gel capsule formulation of SQV at 1,200 mg thrice daily. Saquinavir soft-gel with RTV was studied in a heterogeneous population of 148 HIV-infected patients. Results showed that 91 of 148 subjects (61 percent) achieved and/or sustained undetectable HIV RNA levels (<400 copies/mL) at the completion of 48 weeks of treatment. The efficacy of SQV hard-gel with RTV or SQV soft-gel (with or without RTV-co-administration) has not been compared against the efficacy of antiretroviral regimens currently considered standard of care.

Quoted in a Roche Laboratories press release, Frank Palella (Feinberg School of Medicine, Northwestern University, Chicago) said: "Invirase with ritonavir is an attractive option for the treatment of HIV because it is designed to provide consistently therapeutic levels of saquinavir with twice-daily dosing… Today's news confirms that only low, 100 mg doses of ritonavir are needed to achieve effective levels of saquinavir when given with 1,000 mg Invirase."

Roche Laboratories is developing a 500 mg formulation of Invirase—to be used in the new boosted dosing regimen—with an aim to cut the daily pill count in half. A filing for the 500 mg formulation is projected for submission to the FDA in 2004. ■

Jeffrey Fessel

Vanity Fair readers have every month since 1993 enjoyed *The Proust Questionnaire*, a series of questions posed to celebrities and other famous subjects. In June 2002, *IAPAC Monthly* introduced "In the Life," through which IAPAC members are asked to bare their souls.

This month, *IAPAC Monthly* is proud to feature Jeffrey Fessel, Director of the HIV Research Unit of the Kaiser Permanente Medical Care Program in San Francisco.

What proverb, colloquial expression, or quote best describes how you view the world and yourself in it?
My mother taught me the proverb, "laugh and the world laughs with you; weep and you weep alone." Physicians caring for patients facing a dire prognosis must maintain an optimistic attitude in order to help such patients meet their fate with equanimity.

What activities, avocations, or hobbies interest you? Do you have a hidden talent?
I enjoy playing chess, gardening, listening to music and exploring other cultures, especially ancient ones.

If you could live anywhere in the world, where would it be?
Rome. Italians have a *joie de vivre* like no others, and I love sunshine and Italian food.

Who are your mentors or real life heroes?
Tony Fauci is one of my present-day heroes. He attacked the HIV epidemic with both academic excellence and scientific purity. His efforts enabled the rest of us in record time to put the field of HIV/AIDS on par, scientifically, with all other areas of medicine.

With what historical figure do you most identify?
Albert Schweitzer has been a role model since my earliest days in medical school.

Who are your favorite authors, painters, and/or composers?
Shakespeare, Kandinski, and Schubert. Shakespeare was capable of deepest insight into the human psyche; Kandinski takes us into another world, as do his successors, especially Richter; and I would rather hear a Schubert piano sonata than almost any other music.

If you could have chosen to live during any time period in human history, which would it be?
Although I would have liked to join Schweitzer in Lamberene, I would prefer to be a physician in a future year, say 2150, because by then our profession will be based entirely upon a molecular understanding of illness.

If you did not have the option of becoming a physician, what would you have likely become, given the opportunity?
I was originally intending to be a lawyer (my parents' choice!). Fortunately, at the last moment I saw the light and entered medical school. I have no regrets!

In your opinion, what are the greatest achievements and failures of humanity?
Theism is, at once, humanity's greatest achievement and its greatest failure. Theism imposes the enormous benefit of morality and order upon an otherwise anarchic, amoral society. But the consequences of fanatical theism ("my doxy is orthodoxy, your doxy is heterodoxy!") have in the past been disastrous; and in our own time we are witnessing, worldwide, a repetition of these same sad consequences.

What is your prediction as to the future of our planet one decade from present day?
The melancholy record of human greed, error, and folly will be repeated a thousand-fold in the coming decade and all ills of society will persist. In 10 years' time, the US President will still solemnly pronounce the importance of Africa to the rest of the world just as he did recently, yet Africans will die in double their mortality of today. HIV/AIDS will be contained in the United States, but the epidemic will cause tremendous societal difficulties in China, India, and Russia. Wars, genocide, and fratricide will continue unabated. ■

In a blink of an eye, it seems, Swazis have gone from deep denial of the existence of AIDS to panic as they realise all the people they are burying are not dying of witchcraft. The plethora of AIDS "cures" is a product of that.
AIDS activist Thembi Dlamini, quoted in a January 4, 2004, Bangkok Post *article entitled, "Immunitor Floods Into Swaziland: Firm Denies Exporting Controversial Tablets." Dlamini and other activists in the southern African kingdom of Swaziland are worried about an influx of the controversial product Immunitor V1, manufactured by Thailand's Immunitor Corp. and touted by some as a miracle AIDS cure. Immunitor Corp. claims it had nothing to do with its product's appearance in Swaziland. However, packets of 30 tablets, identified to buyers as "HIV vaccine pills," are selling there for more than the average take-home wage of a Swazi worker. Pharmaceutical regulation is lax in the kingdom, with laws pertaining to the use of medicinal drugs either archaic or unenforced.*

[W]e need to begin addressing how best to assess what the long-term impact of these medications is in our patients. It is critical for both the medical community and the lay community to begin viewing HIV infection as a chronic illness much like diabetes, hypertension, or coronary artery disease.
Ronald B. Reisler, lead investigator of a study published in the December 19, 2003, issue of the Journal of Acquired Immunodeficiency Syndromes, *stating that severe and life-threatening events not related to HIV disease are as important as AIDS as an underlying cause of illness and death in patients on highly active antiretroviral therapy (HAART). According to the researcher and his colleagues at the University of Maryland Medical Center, classic opportunistic infections associated with HIV/AIDS do not account for most of the causes of illness and death in patients on HAART. Reisler et al examined data for close to 3,000 patients on HAART enrolled in five clinical trials over a five-year period. The most common serious events were problems associated with the liver, which occurred in 148 patients. Cardiovascular events carried the highest risk of death.*

Despite the availability of effective HIV therapy, many HIV patients in the US—especially in the inner city—are still in the 1980s.
Joseph J. Pulvirenti, quoted in a December 26, 2003, Reuters Health article, discussing a study of HIV treatment for patients admitted to Cook County Hospital, in Chicago, where he is a staff physician. The study, on which Pulvirenti was lead investigator, appeared in the November 2003 issue of *AIDS Patient Care*. Of 1,562 people living with HIV/AIDS whom the hospital admitted during the three years of the study, less than half were receiving antiretroviral therapy. Pulvirenti told Reuters Health that other factors impact on patients' treatment outcomes, including substance abuse, poverty, and homelessness.

Photo courtesy of Positive Action, GSK

Generations of women sit together to learn about HIV/AIDS during a community gathering held in Addis Ababa.

The more we know about stigma and what it means to women the better we will be able to fight it. The film reflects the situation of Ethiopian women, economically, socially and politically, and this is what we have to change.
Meaza Ashenafi, who heads the Ethiopian Women's Lawyers Association, after seeing the premiere of "Siwir Enba" (or "Hidden Tears"), a new documentary film depicting the suffering of Ethiopian women living with HIV/AIDS. According to a January 6, 2004, United Nations Integrated Regional Information Networks (IRIN) report, the 45-minute film was first shown to government ministers and representatives of non-governmental organizations at a special screening in Addis Ababa. It was then broadcast on state television. Ethiopia's Education Minister Genet Zewde said she was considering using the film as an educational tool in the country's schools.

IAPAC, with its broad mission to improve the healthcare of all who have been affected by the AIDS pandemic, is working to ease suffering and to ensure that persons living with HIV/AIDS are able to live productive lives. Though the battle ahead is one requiring the greatest of global commitments, even small donations from concerned world citizens with the means to provide a small amount of financial assistance can make a notable impact.

The same poverty that engenders higher infection rates in the developing world also means an inadequacy of healthcare infrastructure and, often, the inability of physicians and allied health professionals to access the training and information that they require to effectively treat those in their care.

Sponsor a Developing World Physician

With your donation of US$60 (or more), you can help IAPAC in its mission as an agent of change. For only US$60, IAPAC can sustain the cost of an annual membership for a physician in the developing world, thus enabling physicians in the regions most heavily burdened by HIV disease to gain greater access to critical clinical and policy information and to more fully partake of specialized HIV/AIDS medical training provided in the countries where it is most needed.

For additional information on how you can make a difference, contact Joey Atwell, Director of Membership, at (312) 795-4941 or jatwell@iapac.org, or complete and submit an on-line application at www.iapac.org.

IAPAC physician members recently ranked www.iapac.org:

- **Is the information reliable? YES**
- **Is the Web site easy to navigate? YES**
- **Is the information comprehensive? YES**
- **Is the information clearly presented? YES**

For up-to-the-minute HIV/AIDS information, visit www.iapac.org.