IAPAC Sessions 2002 — Clinicians debate antiretroviral tactics and toxicities, resistance testing, and hepatitis virus coinfection
COVER STORY

IAPAC Drug Guide

The IAPAC Drug Guide (July 2002) features 19 monographs, each a profile of antiretroviral drugs currently used in the clinical management of HIV disease. Each monograph contains recommended dosage, side effect, drug interaction, and pharmacokinetic data. Also included in each monograph are recent updates presented/published within the past 12 months.

DEPARTMENTS

REPORT FROM THE PRESIDENT
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IAPAC Sessions 2002 — Clinicians debate antiretroviral tactics and toxicities, resistance testing, and hepatitis virus coinfection

Mark Mascolini

A faculty of 12 tackled four tough topics at the second annual IAPAC Sessions—PI versus non-PI combos, treatment’s toxicities, resistance testing, and HIV-hepatitis virus coinfection. But that agenda didn’t forestall debate on two other riddles: treatment breaks and when to start.
The eyes of the world will be focused toward Barcelona from July 7-12, 2002, as the Catalonian city hosts the XIV International AIDS Conference.

The global HIV/AIDS community has come to rely on this week of meetings and satellite events as our most critical opportunity to take measure of past successes and future challenges regarding HIV/AIDS care, prevention, and research, as well as advocacy around the host of social, cultural, and economic issues informing our response to HIV disease, and shaping the AIDS pandemic. In this respect, the biennial conference has proved significant in the past in building momentum and synergy around potential solutions to the myriad challenges faced by countless men, women and children living with and affected by HIV/AIDS. Equally important, success has been achieved in the past thirteen conferences in sending clear and forceful messages to global policy-making bodies, funding institutions, and nongovernmental organizations concerning priorities within a basic human rights framework.

As the global community of researchers, care providers, government officials, social activists, and media representatives congregate in Barcelona, it is critical that we ask what has been accomplished in the time that has passed since the XIII International AIDS Conference, held two years ago this month in Durban, South Africa. This is an important step toward ensuring that the XIV International AIDS Conference is a week-long event chock-full with action-filled meaning versus mere rhetorical flourish. In this respect, we should be inspired by the fact that Barcelona has a long and edifying history of testing the accepted sensibilities of the world in which it is surrounded.

Looking back two years, we may recall the XIII International AIDS Conference’s theme, “Break The Silence.” The conference organizers referred to the urgent need to break the silence around equal access to treatment and care; improved and ongoing prevention of HIV transmission; governmental and private sector support of HIV education and resources; human rights; access to appropriate and meaningful information for all sectors; and a supportive environment for people living with and affected by HIV/AIDS. This theme was particularly appropriate for the first International AIDS Conference held in sub-Saharan Africa, since this geographical region accounts for the highest HIV/AIDS morbidity and mortality rates on the face of our planet.

Two years later then, taking heed of what has come to pass since the XIII International AIDS Conference, the question before us must be: Have we broken the silence?

In a number of important regards, the past two years have been monumental. While enough can never be enough in the battle against this insidious disease, there is something both qualitatively and quantitatively special about the political will and financial commitments that the global community has been able to harness over the past two years around many of the aforementioned areas of priority.

Foremost among items of note is the establishment of the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM), whose Board of Directors as recently as April 2002 announced a first round of disbursements. In addition, many governments that had previously lingered in states of denial and confusion around the existence of and factors shaping the epidemics within their national borders, have made solid commitments to establishing national HIV/AIDS programs, including provisions for HIV prevention interventions and access to AIDS care and treatment initiatives. And, we have discovered improved options in antiretroviral treatment for persons living with HIV/AIDS (eg, once-daily dosing of certain antiretroviral drugs). Overall, these are no small accomplishments. Thus, we should applaud the respective efforts of those individuals, institutions, and governments that have made manifest the various priorities and commitments so eloquently articulated at the XIII International AIDS Conference.

Still, while we have indeed traveled a long and productive journey over the past two years, there remain notable imbalances in not only the prevalence of
HIV disease throughout the world, but also in the general means employed as a broad strategy to combat the AIDS pandemic. Though we may have mustered close to US$2 billion in support of the GFATM, for example, we have not overcome the general tendency to favor the less politically challenging HIV prevention focus over initiatives designed to expand access to life-saving and -enhancing treatment. Further, while we have raised our collective voice in demand of commitment from governments and the pharmaceutical industry to ensure better and more affordable treatments, we have not effectively begged the equally important questions: “What happens when these countries do receive these drugs (at discounted rates or free-of-charge (either in branded or generic form))?” And, “Is there adequate infrastructure to support administration of these drugs?” These questions, these imbalances must not be ignored.

As we convene in Barcelona we must recall the theme of the XIII International AIDS Conference, and ensure through compassionate, diligent, and humble service that the echo of complacency does not replace the silence that we have broken. Looking to this critical opportunity to share our lessons and to plan for the future, it is not simply preferable, but rather imperative that we focus upon what and who has been left out of the equations that we have been working with over the past two years.

We must build consensus around ensuring that when drugs are available to populations in need—be they branded or generic—that adequate infrastructure is in place to support their appropriate (and optimal) administration. This includes not only adequate physical infrastructure including a base of clinical and laboratory requirements, but also a full cadre of physicians, nurses, counselors, and allied health professionals who are appropriately trained to administer treatments, each in compliment of the other.

In this respect, we must recommit to examining the host of social, political, and economic factors which work in negative synergy with HIV disease and which have clear implications for both the ability and willingness of patients to adhere to anti-retroviral-based treatments where they are made available.

If we are to find such a balance, then we must endeavor to ensure that physical and financial resources that are collected within the global community through such vehicles as the GFATM, reflect such a balance when they are employed. We cannot afford to shy away from funding treatment and capacity-building initiatives because they raise difficult political questions and/or because we fear the risk of offending. Rather, we must look to this challenge of building consensus around appropriate treatment in the same steadfast, unflinching manner in which we did almost a decade ago when our hopes of caring for patients with “effective” treatments remained a dream.

The agenda does not end there. With Spartan-like determination, we must continue to find creative and efficacious means of raising the necessary funds to guarantee provision of HIV prevention and treatment programs throughout the world with a view to realizing the public health dictum of health for all.

We have before us in July 2002 the rare opportunity to meet, share, and plan with a view to combating HIV disease in an expanded and strategic manner. Based on 20-plus years of history, we have every reason to believe that our global HIV/AIDS community is capable of mounting such a renewed, bolstered assault. The International Association of Physicians in AIDS Care (IAPAC) is mobilized for this opportunity. IAPAC is willing and able to serve as a partner in our collective efforts to battle complacency that serves to thwart our progress, and to advance commitment around robust and appropriate responses to this global pandemic. It is with this vision of collective energy, and on behalf of IAPAC’s more than 12,000 members in 89 countries, that I welcome delegates to the XIV International AIDS Conference. I hope that the theme of this year’s conference—“Knowledge and Commitment for Action”—resonates throughout the week’s activities. And, I pray that our time spent together over this week will yield what may some day soon come to be appreciated as tangible solutions that contributed to the end of the HIV/AIDS pandemic.

José M. Zuniga is President of the International Association of Physicians in AIDS Care and Editor-in-Chief of the IAPAC Monthly.
Faculty member Richard Haubrich and IAPAC Sessions 2002 Chair Renslow Sherer share a light moment between morning and afternoon sessions May 17, 2002.

David Katzenstein delivers a presentation on the limitations of antiretroviral drug resistance testing in HIV clinical management.

Olga Wildfeuer, a New York delegate, listens to a discussion about HIV-HCV co-morbidity led by faculty member Maurizio Bonatini.
How should patients be monitored over time for possible metabolic and morphologic abnormalities seemingly associated with antiretroviral therapy?

As issues such as antiretroviral drug burden appear to be resolving themselves (eg, once-daily dosing), what regimens are best used as initial HIV therapy?

Unexpected, contradictory antiretroviral resistance test results are common; how should clinicians manage these problems?

What should clinicians do to diagnose and manage HIV coinfection with HBV and/or HCV?

These are some of the important questions asked, answered, and debated by HIV/AIDS thought-leaders from throughout the United States who attended the IAPAC Sessions 2002, which was hosted May 16-17, 2002, by the International Association of Physicians in AIDS Care (IAPAC).

The IAPAC Sessions 2002, which were chaired by longtime IAPAC member Renslow Sherer, focused on the practical arena of HIV management. Invited faculty, delegates and observers—the majority IAPAC members—addressed four areas of clinical uncertainty: metabolic/morphologic complications associated with antiretroviral therapy; utilization/sequencing of antiretroviral drugs; antiretroviral drug resistance testing in HIV clinical management; and HIV and Hepatitis B/C co-morbidity and treatment.

Faculty for the IAPAC Sessions 2002 included Maurizio Bonacini (University of Southern California); Richard Haubrich (University of California, San Diego); Diane Havlir (University of California, San Diego); David Katzenstein (Stanford University School of Medicine); Daniel Kuritzkes (University of Colorado Health Science Center); Barbara McGovern (New England Medical Center); Kathleen Mulligan (University of California, San Francisco); Stuart Ray (Johns Hopkins University School of Medicine); Renslow Sherer (Rush Medical College); Kimberly Smith (Rush-Presbyterian-St. Luke’s Medical Center); Pablo Tebas (Washington University School of Medicine); and Christine Wanke (Tufts University School of Medicine).

According to IAPAC President José M. Zuniga, IAPAC plans to host the IAPAC Sessions next year in France, South Africa, and the United States—with special emphasis on debates relevant to the respective geographical regions.

The IAPAC Sessions 2002 were made possible through unrestricted educational grants from Abbott Laboratories; Bristol-Myers Squibb-Virology; Gilead Sciences; GlaxoSmithKline; Ortho Biotech; Roche Pharmaceuticals/Trimeris; Schering-Plough; and Tibotec-Virco.
(Clockwise from top left) Irene Maina and Alawode Oladele, both delegates from Georgia; and Drew Kovach, a Hawaiian delegate.

Pablo Tebas dissects data regarding metabolic abnormalities encountered in some patients on HAART.

Washington, DC, delegate Franco Lori questions data presented on once-daily dosing of HIV medications.
Kimberly Smith enjoys a running joke with her co-presenter about their “opposing” views regarding PI-containing versus PI-sparing regimens.

Kathleen Mulligan reiterates a point about morphologic complications associated with antiretroviral drug therapy.

Stuart Ray (forefront) and Maurizio Bonacini listen to a presentation by Barbara McGovern on treatment of HIV-HCV coinfection.

David Wheeler, a Virginia delegate, volunteers his clinical experience using antiretroviral drug resistance testing.
First-time visitors to the University of Chicago’s Gleacher Center, Room 200, may get the vague sense that they’ve seen this place before—perhaps in certain circa-1600 oil paintings. More than anything, Room 200 looks like a 21st century reimagining of a 17th century surgery, those steeply banked semicircles where medicine’s initiates, and the merely curious, gathered to watch the day’s deans dissect cadavers—or less fortunate live specimens—for their edification.

Something very much like that happened on May 16-17, 2002, in Chicago, when the International Association of Physicians in AIDS Care (IAPAC) gathered some of this era’s top HIV thinkers and asked them to anatomize four specimens before an eager crowd. And the specimens were very much alive, and expertly vivisected through not human, mammalian, or even Drosophilian, but rather conceptual.

In anatomy lessons led by Christine Wanke (Tufts University, Boston), Diane Havlir (University of California, San Diego), Daniel Kuritzkes (Brigham and Women’s Hospital, Boston), and Maurizio Bonacini (California Pacific Medical Center, San Francisco), a faculty of eight pared away superficial tissue and probed the tendons of four topics: antiretroviral tactics, their metabolic and morphologic side effects, resistance testing, and the confluence of HIV with hepatitis B and C viruses.

The IAPAC Sessions 2002 differed from classically limned anatomy lessons in another important way: Although the audience included a sprinkling of the merely curious, most attendees were anything but acolytes in HIV medicine. They were carefully selected clinicians seeing large quotas of people with HIV, and imbued with a matching commitment to the corpus of complication and contingency that defines the art in this science.

The pit and the pendulum

Without a doubt, Diane Havlir essayed the most provocative exercise in the Gleacher Center’s anatomy pit when she squared up to the when-to-start pendulum, now arcing deeper and deeper into “later’s” nether regions. Havlir evinced no data to challenge the hit-later standard of care, but rather offered a critique of pure reason.

The reasons to treat later in the course of HIV progression, somewhere below 350 cells/mm³, but if possible above 199 cells/mm³, are familiar to all: The risk of progression is low even when treatment starts late, Havlir allowed, and later intervention does not greatly jeopardize the response to treatment. Antiretroviral regimens are tough to stomach and hard to stick with—traits that favor missed doses and foster resistance. And then there is toxicity.

But Havlir challenged two key cohort studies that showed low risks of progression or death when therapy starts below 350 cells/mm³. These studies in Vancouver and at Johns Hopkins in Baltimore, which both tracked treated people beginning in 1996, appraised antiretroviral regimens more than a tad moldy by today’s standards. So they fail to reflect the possible benefits of starting with a nonnucleoside (NNRTI) regimen, for example, or with a boosted protease inhibitor (PI). As a result, the rationale for later treatment, as framed now, overlooks the greater simplicity and tolerability of newer therapies, the profusion of salvage options, and a changing patient population: Those starting treatment in the past few years don’t lug the baggage of sequential nucleoside (NRTI) monotherapies and duotherapies, or the class-sacrificing stratagem of adding a new inhibitor to a woebegone combo.

Follow-up in the Vancouver and Baltimore studies, 28 and 22 months, now represents a small fraction of the expected life span made possible by today’s best combinations. If these cohorts could be tracked for even a few more years, Havlir proposed, differences in survival or AIDS diagnoses may emerge. Even if continued follow-up discerned no great morbid or mortal difference between early and late starters, she argued that an endpoint focus narrowed to AIDS or death blurs other potential benefits of early intervention—lower incidence of HIV-related (though not AIDS-defining) diseases, increased energy and a better quality of life, enhanced cognition and performance, and greater prospects of...
benefiting from strategies that may work better in a better preserved immune system, such as therapeutic vaccines.

What about antiretroviral toxicity? That “major concern,” Havlir conceded, lingers. The full spectrum of side effects exceeds our field of vision, and their mechanisms remain murky. They may not be treatable; they may not be reversible. And there’s the rub for many clinicians seeing a person with newly diagnosed HIV infection, a CD4 count of 325 cells/mm³, and a viral load of 60,000 copies/mL. If she had the time, Havlir might have dwelled more on the better tolerability of new drugs—the antiatherogenic potential of nevirapine,3 for example, or of the investigational PI atazanavir,4,5 not to mention the durability or endurability that have made efavirenz a first-line winner in cohort after cohort.6-8

Although plenty more clinical research must address these maladies—and she urged clinicians to put affected people in toxicity trials—Wanke noted that even early studies suggest means to counter some bedeviling side effects (Table 1).

Antiretrovirals, with PIs topping the list, deserve an ample share of blame for dysregulated lipids and glucose in people being treated for HIV. But Kathleen Mulligan (University of California, San Francisco) reminded attendees that the retrovirus itself starts stirring the metabolic pot well before HIV drugs spice the stew. It’s been 10 years since Mulligan’s colleague Carl Grunfeld charted higher triglycerides in people with HIV infection or AIDS than in infected people.9 In the same study total cholesterol—including both the high- and low-density lipoprotein varieties (HDL and LDL)—proved significantly lower in people with AIDS. When people started taking PIs, triglycerides climbed even more, total and LDL cholesterol shot up, and protective HDL cholesterol stayed low.

In healthy volunteers taking ritonavir, research showed marked jumps in triglycerides and cholesterol, striking in their rapidity and (for triglycerides) their magnitude.10 Indinavir given to healthy people for 4 weeks barely budged triglycerides, total cholesterol, or LDL cholesterol,11 but it did rile glucose, and quickly (see below). Other work documented significantly impaired endothelial function in people taking PIs.12 Research also showed thicker carotid artery walls in HIV-infected women with lipodystrophy13 and more plaques gumming up carotid and femoral arteries in people with HIV,14 but PIs didn’t worsen either of these cardioconsequential omens.

Do these talismans—favorable, unfavorable, and indeterminate—portend a heart disease epidemic in people taking PIs? Mulligan summoned siftings from two massive cohorts in an attempt to answer that question, and so far (if one looks only at those studies) the answer is no. After 5.5 years and 14,823 person-years of follow-up in a California health cooperative, people with HIV had higher rates of coronary heart disease ($P = 0.003$) and myocardial infarction ($P = 0.07$) than did uninfected people.15 But neither antiretrovirals in general nor PIs in particular weighed in this equation. A Veterans Administration study embracing 121,936 person-years of follow-up logged decreased hospital admissions for heart disease and stroke since PIs took the stage.16 But this second survey did not compare HIV-infected and uninfected people, Mulligan observed. And the drops in admissions may reflect unmeasured factors, such as better controlled chronic infection in people taking potent antiretrovirals.

Those findings don’t mean people taking protease drugs and doctors who prescribe them can forget about heart attacks, Mulligan cautioned. Rather she stressed one sure bet in warding off time in the cardio ward—a renewed focus on reducing or eliminating known risk factors.

In bygone days before one ever worried about whether to say protease or protease, HIV had little measurable impact on glucose or insulin.17 If anything, Mulligan noted, insulin sensitivity seemed better in people infected with HIV than in seronegatives. But all that changed when PI prescribing began. She listed four studies that cataloged higher rates of impaired glucose tolerance or diabetes in PI takers or people with lipodystrophy.18-21 (Table 2).

If a heart disease epidemic does not yet plague people taking PIs, does a diabetes epidemic? Mulligan observed that the smaller studies listed in Table 218,19 are not the only ones showing double-digit diabetes rates in HIV-infected people. Three large cohorts had rates ranging from 10 to 14 percent in HIV-infected people,22-24 and up to 19 percent in people coinfected with HIV and HCV.24 One of these surveys22 studied only people taking PIs, while the other two23,24 traced no links between PIs and diabetes. But Mulligan said a rising incidence of diabetes in PI takers wouldn’t surprise her because cohort studies show that these drugs bollix glucose metabolism (Table 2), and other research verifies that PIs destabilize glucose homeostasis.

Several studies in the past few years drive those points home, and the dysregulating derelicts include indinavir,11,25-27 ritonavir,27 amprenavir,27 and nelfinavir—so far. The only study to implicate amprenavir in insulin resistance did so in fat cells,27 whereas an eight-week amprenavir trial in whole humans found no insulin resistance.28 Mulligan added that atazanavir may also escape the taint of muddled glucose transport, but that finding remains to be verified in humans.

Although PIs that induce insulin resistance do so rapidly—in people with or without HIV infection—visceral fat gains that come with continued PI therapy only

### Table 1. When antitoxicity measures may be warranted

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Possible interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat atrophy</td>
<td>Antiretroviral switches, rosiglitazone, cosmetic surgery</td>
</tr>
<tr>
<td>Fat accumulation</td>
<td>Diet, exercise, metformin, recombinant human growth hormone</td>
</tr>
<tr>
<td>Glucose abnormalities</td>
<td>Diet, exercise, glitazones, antiretroviral switches</td>
</tr>
<tr>
<td>Lipid abnormalities</td>
<td>Diet, exercise, antilipid agents, antiretroviral switches</td>
</tr>
</tbody>
</table>

Source: Christine Wanke.
546 people with HIV found that atrophy (see above). This 21-month analysis of weighing only AIDS diagnoses and death therapy has risks not measured in studies Diane Havlir's contention that delaying the prism of nadir and maximum CD4+ tightened this link in a survey that looked HIV Outpatient Study (HOPS) investigators across studies is the one between more could sort out subtle cases.

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short for high cholesterol, and fibrates for
• Improve strength
• Decrease total and abdominal fat
• Improve insulin sensitivity
• Improve glucose tolerance
• Increase HDL cholesterol
• Increase muscle mass
• Improve endurance
• Improve strength

If it could be bottled, everyone would pre-
scribe it.

Morphometabolic treatment options
Kathleen Mulligan unrolled a laundry list of factors that promote diabetes or coronary heart disease. She cited 17, plus one grab bag of “emerging factors.” One of them can’t be changed — family history and age. Statins that don’t have unseemly interactions with PIs continue to be studied for high cholesterol, and fibrates for high triglycerides. But Mulligan stressed that so-called lifestyle changes — though much harder to swallow than HMG CoA reductase inhibitors — can yield a world of benefit at essentially no risk. The well-
known big four deserve all the practical support clinicians can muster: smoking cessation, diet, weight reduction, and exercise (perhaps in the less threatening guise of “increased physical activity”). In people without HIV, Mulligan noted, exercise alone can:

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Population</th>
<th>n</th>
<th>Diabetes (%)</th>
<th>IGT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walli (1998)18</td>
<td>Taking PIs</td>
<td>24</td>
<td>37</td>
<td>17</td>
</tr>
<tr>
<td>Behrens (1999)13</td>
<td>Taking PIs</td>
<td>38</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td>Carr (1999)14</td>
<td>Taking PIs</td>
<td>113</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Hadigan (2000)32</td>
<td>With lipodystrophy</td>
<td>71</td>
<td>7</td>
<td>35</td>
</tr>
</tbody>
</table>

*2-hour glucose ≥200 mg/dL.
†2-hour glucose ≥140 mg/dL.

Sources: Kathleen Mulligan.

Fat where you don’t want it, and not where you do
Pablo Tebas (Washington University, St. Louis) launched his survey of bad body shape changes by lamenting the “rather complicated” case definition backed by the European Medicines Evaluation Agency (EMEA) and presented earlier this year.30 With 10 factors in the equation (see note 31), the proposed definition attains a sensitivity of 79 percent and a specificity of 80 percent.

Tebas suggested the definition will find its greatest use as a benchmark for clinical investigation. Yet the 31-site, 1,000-person effort may prove clinically useful as well, because the research team will soon offer an easy-to-use online version of their equation. Clinicians will be able to plug in a person’s data for all or some of the variables and get a lipodystrophy score that could sort out subtle cases.

One correlation that seems to hold true across studies is the one between more advanced HIV disease and fat abnormalities. HIV Outpatient Study (HOPS) investigators tightened this link in a survey that looked specifically at lipatrophy incidence through the prism of nadir and maximum CD4+.

Counts.32 Their findings lend credence to Diane Havlir’s contention that delaying therapy has risks not measured in studies weighing only AIDS diagnoses and death (see above). This 21-month analysis of 546 people with HIV found that atrophy appeared in only 3.3 percent of those whose CD4+ tally never fell below 350 cells/mm3, but atrophy plagued 12 percent with a nadir between 200 and 349 cells/mm3, and more still with nadirs below 200 cells/mm3, even if their CD4+ counts rose above 350 or 500 cells/mm3 with treatment.

The HOPS cohort consists largely of men, but women may be more prone to lipodystrophy — or at least fat accumulation — than men. Female gender was an independent risk factor in the EMEA case definition.30 And in an Italian cohort of 2,258 people with HIV, including 677 women, female gender proved the strongest predictor of fat abnormalities with an adjusted odds ratio of 2.019 (P = 0.001).31 Significantly more women (10.1 percent) than men (7.7 percent) in this cohort had fat accumulation (P = 0.0008), and significantly more women (22.4 percent) than men (9.7 percent) had both accumulation and atrophy (P = 0.0001). More men than women had atrophy alone, but this difference lacked significance.

Table 2. Diabetes and impaired glucose tolerance (IGT) in the age of PIs

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• Improve strength
• Decrease total and abdominal fat
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• Increase HDL cholesterol
• Increase muscle mass
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to randomized trials and one nonrandomized study hold true. In one randomized study, three groups charted small decrease in limb fat gain (10%) with the drug cut visceral fat and shrank buffalo humps in open-label studies. Christine Wanke noted. But the dose used for wasting, 1 mg daily. The other common side effect of growth hormone, swelling, can be painful and can be mistaken for reversal of atrophy. Finally, the drug’s effect is transient, so it would have to be started again when the effect wears off.

Table 3. Peripheral fat gains in three drug-switch studies

<table>
<thead>
<tr>
<th>Author, design</th>
<th>DEXA results</th>
<th>CT results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cart et al. randomized (n = 111 x 24 w) 41</td>
<td>0.39 kg limb fat gain (10%)</td>
<td>Improvement</td>
<td>No participant or clinician noticed any fat gain</td>
</tr>
<tr>
<td>John et al. randomized (n = 39 x 24 w) 42</td>
<td>0.018 kg/month fat gain in arms; 0.013 kg/month fat gain in legs</td>
<td>Not done</td>
<td>No lipid improvements</td>
</tr>
<tr>
<td>McComsey et al. nonrandomized (n = 118 x 24 w) 43</td>
<td>25% fat gain in arms, 6% in legs, and 9% in trunk</td>
<td>Improvement</td>
<td>Participants self-reported fat gains</td>
</tr>
</tbody>
</table>

ABV = abacavir; CBV = Combivir (AZT/3TC).

- The Finnish study lasted only 24 weeks, while people continued to take drugs likely to contribute to lipodystrophy. The Australian trial will last 48 weeks.
- With only 15 people per study arm, the trial was powered to detect a 40 percent increase in limb fat, which would have been an astonishing gain. The Australian trial will enroll 100 people.
- The study groups were not well balanced for limb fat at entry.
- The Finnish study used MRI to measure fat changes, whereas DEXA is the preferred imaging technique and the one the Australians will use.

Tebas added that the 8-mg rosiglitazone dose used in the Finnish study seems adequate, but it was given once daily instead of in twice-daily 4-mg doses, which may work better.

In the end clinicians may not need glitazones to remedy lipoatrophy, not if results of three drug-switch studies hold true. In two randomized trials and one nonrandomized study, three groups charted small but significant limb fat gains after switching from stavudine (d4T) to another NRTI or from two NRTIs—d4T and lamivudine (3TC) or zidovudine (AZT) and 3TC—and a PI to abacavir plus Combivir (AZT/3TC) (Table 3).

Tebas tempered any enthusiasm these results may inspire by noting that both the studies and the fat improvements were small—so small that people in the 24-week Australian trial and their clinicians didn’t notice the fat gain. 41 Perhaps the most hopeful finding came from the other Australian study, which showed that fat gains in arms and legs continued from week 24 through 48. ACTG 5110 will pursue this strategy, randomizing people to trade in d4T or AZT for either an NNRTI/PI regimen or for abacavir plus the baseline PI or NNRTI.

Swapping d4T or a PI for different drugs may slowly promote subcutaneous fat gains in arms and legs but appears to do nothing to replace lost facial fat. Tebas briefly mentioned early studies of polylactic acid (New-Fill) facial implants, saying “the aesthetic result is remarkable.” This promising technique remains unavailable in the US.

Kathleen Mulligan and others continue their struggle to find a tolerable yet still effective dose of recombinant human growth hormone (Serostim) for lipodystrophy. The drug cut visceral fat and shrank buffalo humps in open-label studies. Christine Wanke noted. But the dose used for wasting, 6 mg daily, far exceeds what’s needed for lipodystrophy. Mulligan and colleagues found that even 3 mg daily upsets glucose homeostasis, 44 and they are now evaluating 1 mg daily. The other common side effect of growth hormone, swelling, can be painful and can be mistaken for reversal of atrophy. Finally, the drug’s effect is transient, so it would have to be started again when the effect wears off.

Are PI s destined for second-line duty?
The second major topic at the IAPAC Sessions 2002—whether to start treatment with a PI-sparing regimen—has an obvious impact on the first topic—averting or reversing toxicities. Protease inhibitors contribute to, or plainly cause, all of the toxicities reviewed in the first part of this article. Pablo Tebas argued that they have more than a little to do with osteopenia, though that proposition remains contentious. So Kimberly Smith (Rush Presbyterian-St. Luke’s Medical Center, Chicago) seemed to have the easier task in arguing against PIs in a person’s first regimen. But Renslow Sherer (Cook County Hospital, Chicago) scored more than a few points for entrenched PI enthusiasts.

Smith made three arguments for non-PI regimens: (1) Their efficacy equals or exceeds that of PI combos. (2) They cause fewer metabolic side effects. (3) They improve adherence. DuPont’s seminal 006 study showed that efavirenz outmatched standard-dose indinavir in treatment-naive people, 46 and it maintained that edge through 96 weeks. 47 Nevirapine plus Combivir did as well as twice-daily nelfinavir plus Combivir in keeping viral loads below 20 copies/mL through 12 months in a naïve population. 47 And abacavir plus Combivir more than held its own against indinavir plus Combivir for 48 weeks in another naïve cohort. 48

This last study underlined an earlier concern about triple-nuke regimens, their suspect performance in people starting therapy with a high viral load. In an as-treated analysis 59 percent in the abacavir arm versus 73 percent in the indinavir arm with a baseline viral load over 100,000 copies/mL had fewer than 50 copies/mL at week 48. But an intent-to-treat analysis discerned no RNA difference between these two groups. Another trial comparing abacavir/Combivir with nelfinavir/Combivir found equivalent proportions with sub-50-copy viral loads in the two arms in a 48-week missing-data-equal-failure analysis. 49 But Smith observed that researchers designed this trial to compare lipid changes in treatment-naive people (half of them women) and not to compare virologic outcomes. The 48-week viral load results involved only 15 people taking abacavir and 19 taking nelfinavir.

Smith did not broach the growing hoard of cohort data supporting first-line efavirenz regimens. If she had time, she might have mentioned that efavirenz outpaced PIs 6,8 (including ritonavir/ saquinavir) in suppressing viral load, at least over the short term. The potency and tolerability of NNRTIs swayed the British HIV Association to list them as “recommended” for first-line therapy, while advising that PIs may be “considered” up front. 50 The latest US Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents give efavirenz the
nond as a first-line option, but not nevirapine. They also put indinavir, nelfinavir, and three dual PIs in the first-line column. Renslow Sherer, assigned to defend PI therapy, nonetheless proposed abacavir and nevirapine as first-line cornerstones, a concession demonstrating the allure of starting with a non-PI combo.

But Sherer also reviewed trial data suggesting that two PIs may constrain the virus longer than efavirenz. Although efavirenz bettered ritonavir/saquinavir virologically in one eight-month cohort study, a four-year intent-to-treat follow-up of people taking those two PIs counted 70 percent of single PIs (Figure 1, left). Those low troughs, perhaps deepened by missed doses, allow resistance mutations to pop up one after another. NNRTIs, in contrast, have comfortably safe, high troughs. But the comfort zone can shrink fast because only one or two mutations will overwhelm efavirenz or nevirapine (Figure 1, middle). Several mutations must evolve to sink boosted PI combos (Figure 1 right), which notch troughs much higher than single PIs. This picture could change again, though, if second-generation nonnukes fulfill the promise to erect a higher barrier to resistance than their first-generation forebears.

Pressing the resistance argument further, Sherer cited a revealing but small study comparing the impact of up-front regimens on later resistance profiles. This analysis of 47 treatment-naïve people starting triple therapy with a PI and 17 starting with an NNRTI found that 41 percent taking an NNRTI versus 6 percent taking a PI ended up with dual-class resistance if their viral load rebounded above 1,000 copies/mL. Those results suggest that resistance to NRTIs may evolve more quickly when an NNRTI fails than when a PI does.

Convenience and toxicity: no contest?

An oft-evoked argument favoring NNRTIs is their greater convenience and tolerability when compared with PIs, virtues that should translate into tighter adherence and thus longer viral suppression. But the convenience edge seems a lot shakier now that people are taking twice- or even once-daily boosted PIs instead of indinavir or nelfinavir three times a day.

When Kimberly Smith outlined the traits of complex regimens—thrice-daily dosing, a high pill burden, food and fluid requirements, and special storage needs—she could have made a good case against solo indinavir, amprenavir, or ritonavir. But how often are those PIs prescribed alone nowadays? She also cited week 44 to 48 self-reported adherence data from the trial comparing abacavir/Combivir with indinavir/Combivir. Significantly more taking abacavir (72 percent) than indinavir (45 percent) claimed better than 95 percent adherence ($P < 0.001$). But again that study used three-times-daily indinavir.

Renslow Sherer brought this contest up to date when he compared a few PI combos now in vogue with standard NNTRI dosing. Lopinavir/ritonavir (three pills twice daily) and indinavir/ritonavir (three pills twice daily) don’t suffer much from comparison with nevirapine (one pill twice daily) or efavirenz (one or three pills once daily). He observed that research has yet to nail down an adherence advantage for once-daily versus twice-daily dosing. So the question becomes how much sheer pill number affects adherence. Analysis of 23 clinical trials tied higher pill burden to worse 48-week virologic control. But this analysis found no virologic difference between regimens centered on a PI, an NNRTI, or an NRTI, and it evaluated no double or boosted PIs.

Smith made a strong case for greater safety with abacavir, efavirenz, and nevirapine than with PIs, especially when it comes to lipids and glucose. Indeed, her toughest task in this part of the debate must have been picking from the profusion of studies that back her points. She cited the trial comparing abacavir/Combivir with nevirapine (one pill twice daily) or efavirenz (one or three pills once daily). She also cited week 44 to 48 adherence data from 48 self-reported adherence data from 48 self-reported adherence data. But how often are those PIs prescribed alone nowadays? She also cited week 44 to 48 self-reported adherence data from the trial comparing abacavir/Combivir with indinavir/Combivir. Significantly more taking abacavir (72 percent) than indinavir (45 percent) claimed better than 95 percent adherence ($P < 0.001$). But again that study used three-times-daily indinavir.

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Smith also invoked results of two randomized trials in which people traded a PI for abacavir, nevirapine, or efavirenz. Triglycerides fell most in the nevirapine groups, which also enjoyed the sharpest jumps in HDL cholesterol. The biggest drops in total cholesterol came in the abacavir groups. The studies also mapped significant declines in insulin resistance. The abacavir groups suffered the most virologic breakthroughs, which researchers tied to baseline reverse transcriptase mutations.

![Figure 1. Trough levels and evolution of resistance to PIs and NNRTIs](image-url)
Sherer could only concede that faulty metabolic markers start falling back in line when people stop PIs. He cited an outline of switch studies by William Powderly (Washington University, St. Louis) summarizing lipid and insulin improvements with nevirapine, efavirenz, or abacavir (Table 4). But Sherer worried that “we’re too obsessed with lipids, out of proportion to other issues affecting people in our care.” Besides a welter of deranged lipids and glucose, he reminded attendees, PIs can also induce nausea, diarrhea, kidney stones, and liver toxicity. On the nonnuke side of the ledger, he listed rash and liver toxicity for nevirapine and efavirenz, and central nervous system toxicity. On the nonnuke side of the ledger, he listed rash and liver toxicity for nevirapine and efavirenz, and central nervous system toxicity.

The lipid obsession, Sherer added, will prove unfounded if a theory advanced by Werner Richter (Ludwig-Maximilians-University of Munich) is right. Richter holds that the very low-density lipoprotein (VLDL) and apolipoprotein B patterns conjured by the liver in people with PI-induced hyperlipidemia resemble those of people with familial hypertriglyceridemia, not those of people with familial combined hyperlipidemia. What’s the difference? Familial combined hyperlipidemia confers a high risk of heart disease, while familial hypertriglyceridemia confers no risk or a low risk of heart disease. If true, that hypothesis could partly explain why two big cohort studies failed to forge a link between PIs and heart disease.15,16

### Is resistance testing a waste of time?

An informal poll of clinicians attending the IAPAC Sessions 2002 showed that most use genotyping to plan therapy, a few use phenotyping, and perhaps a surprise — more than a few use Virtual Phenotyping, the Virco system that predicts susceptibility of a virus to antiretrovirals based on an always-growing database of viruses with the same mutations. But before this endorsement of resistance assays lie persistent uncertainties about when to use these tests and what they mean. Those uncertainties bedevil not only front-line HIV clinicians, but also the experts, as David Katzenstein (Stanford University), Richard Haubrich (University of California, San Diego), and session chair Daniel Kuritzkes (University of Colorado Health Science Center) made clear.

Assigned to probe the limits of resistance testing, Katzenstein averred that, despite such limits, he sees these tests as a crucial component of antiretroviral planning. Assigned to stress these assays’ merits, Haubrich spent much of his time explaining why they fail.

Katzenstein and Haubrich agreed wholeheartedly on one point: as HIV therapies improve, it’s getting harder and harder for randomized trials to show a significant virologic benefit for resistance testing. Haubrich told this tale of diminishing returns in a concise table60-67 (Table 5). The difference in RNA drop between the genotyping arms and standard-of-care arms in the first two randomized resistance studies, VIRADAPT and GART, came close to 0.6 log. But the difference between the assay arm and the control arm in all the following studies averaged 0.06 log.

Haubrich saw two reasons for this tailspin: Salvage options today are more plentiful and more potent than they were in the infancy of resistance testing. As one attendee aptly noted, genotyping in VIRADAPT and GART might have proved less advantageous if clinicians in both arms could have prescribed lopinavir/ritonavir along with, say, tenofovir. Haubrich’s second point was that clinicians picking rescue regimens in the standard-of-care arms are doing a much better job these days. Analyzing his own phenotyping study, CCTG 575,67 he noted that the lack of difference between study arms (Table 5) shows “not that phenotyping failed, but that standard-of-care did so well.” But if clinicians have become so savvy in picking rescue drugs, Kuritzkes wondered, what does phenotyping add?

There are other ways to analyze the results in Haubrich’s resistance assay timeline (Table 5). One is that phenotyping has failed in three62,64,67 of four studies. The only study in which it passed muster, VIRA 3001,63 had the least treatment-experienced population. Those results run counter to the idea that genotyping works best in people with a short history of treatment failure, while phenotyping works best in those with a long history. As Kuritzkes explained this concept, after a first or second PI failure, genotyping will pick out the sentinel mutations and so suggest salvage options. But after several PI failures, the hash of primary and secondary protease mutations becomes too hard to decipher. At that point a phenotype may tell you more. But how much more? Katzenstein

### Table 4. Metabolic changes in PI-to-non-PI switch studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>First PI failing at entry (%)</th>
<th>Log change in HIV RNA (w 12-16)</th>
<th>&lt;400 copies/mL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIRADAPT10</td>
<td>G vs SOC</td>
<td>40</td>
<td>-1.04 vs -0.46*</td>
<td>29 vs 14*</td>
</tr>
<tr>
<td>GART11</td>
<td>G vs SOC</td>
<td>50</td>
<td>-1.19 vs -0.61*</td>
<td>34 vs 22*</td>
</tr>
<tr>
<td>Kaiser12</td>
<td>P vs SOC</td>
<td>25</td>
<td>-0.25 vs -0.4 (NS)</td>
<td>NA</td>
</tr>
<tr>
<td>VIRA 300163</td>
<td>P vs SOC</td>
<td>100</td>
<td>-1.23 vs -0.87*</td>
<td>46 vs 34 (NS)</td>
</tr>
<tr>
<td>NARVA14</td>
<td>P vs G vs SOC</td>
<td>&lt;30</td>
<td>-0.7 vs -1.1 vs -1.0</td>
<td>34 vs 41 vs 34</td>
</tr>
<tr>
<td>ARGENTA15</td>
<td>G vs SOC</td>
<td>47</td>
<td>-0.6 vs -0.4 (NS)</td>
<td>26 vs 12*</td>
</tr>
<tr>
<td>Havana66</td>
<td>G vs SOC</td>
<td>44</td>
<td>-1.5 vs -1.2*</td>
<td>66 vs 53*</td>
</tr>
<tr>
<td>CCTG 57567</td>
<td>P vs SOC</td>
<td>80</td>
<td>-0.7 vs -0.7 (NS)</td>
<td>45 vs 46 (NS)</td>
</tr>
</tbody>
</table>

G = genotyping; NA = not applicable; NS = not significant; P = phenotyping; SOC = standard of care.

* P < 0.05.

† At 12 months.

Source: Richard Haubrich.

### Table 5. Is the resistance assay advantage waning with time?

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G = genotyping; NA = not applicable; NS = not significant; P = phenotyping; SOC = standard of care.

* P < 0.05.

† At 12 months.

Source: Richard Haubrich.

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proposed that, if (as trials show) phenotyping gives you at best a marginal edge, it may not be worth paying up to three or four times more than you would pay for a genotype.

Another complication in analyzing the randomized trials on record, Katzenstein observed, is that most of them have short follow-ups, generally 12 to 16 weeks. The longest study, CCTG 575, showed a virologic dead heat between phenotyping and no phenotyping after 12 months. Would genotyping’s advantage vanish if follow-up continued so long? Perhaps not, if 48-week results of the 1997-1998 VIRADAPT study hold true in 2002.

Short-term endpoints, Katzenstein said, can be “contaminated” by expert opinion. And that’s what some people say happened in GART.61 Prescribers in that study didn’t get raw genotypes; they got genotypes interpreted by virologists who spend most waking hours thinking about resistance. So, this argument goes, taking away the experts may take away genotyping’s advantage.

The more recent Havana study bolsters that argument. This trial randomized people taking a failing regimen to get new drugs based on genotyping, expert advice, both, or neither.62 Genotyping raised the odds of a good response 1.7 times \((P = 0.016)\), but failure of a second regimen sliced the odds of success by 60 percent \((P = 0.057)\), and a third failure cut the odds of success by 70 percent \((P = 0.0001)\). For people coming off their second failed regimen, though, expert advice tripled the chance of virologic success \((P = 0.016)\). In other words, when things get tricky, call an expert.

But if you can tap expert opinion, do you even need a genotype? Or, to put it another way, if one adds up all these trends, do they mean resistance testing is a waste of time? No one ventured that opinion, but Haubrich and Katzenstein took a hard look at when testing does make sense (Table 6). Both were less gung-ho than the IAS-USA panel that issued guidelines in 200069 and a bit less enthusiastic than DHHS experts who offered advice earlier this year.51 Though Haubrich didn’t endorse testing for treatment-naïve people, he said that could change in the future if transmission of resistant virus continues to rise (as it is already in some parts of North America and Europe). But in untreated people diagnosed simultaneously with HIV and their first AIDS-defining illness, he saw little use for resistance testing. At that point, Haubrich explained, any resistant virus transmitted during primary infection will have reverted back to wild type.

Kuritzkes cast the question of testing treatment-naïve people in monetary terms. If paying is no problem, testing all naïve people seems reasonable because you will pick up a few transmitted mutations. But early research suggests that testing a naïve population becomes cost effective only when at least 5 percent of that population \((P = 0.0001)\) got infected with resistant virus.

**Tables 6. Evolving advice on when to test for resistance**

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary infection</td>
<td>Consider</td>
<td>Consider</td>
<td>Uncertain</td>
<td>Perhaps in future</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>Consider</td>
<td>Not generally recommended</td>
<td>Probably not</td>
<td>Perhaps in future, but only if infection is recent</td>
</tr>
<tr>
<td>First regimen failure</td>
<td>Recommended</td>
<td>Recommended</td>
<td>Yes, though rationale diminishing</td>
<td>Yes</td>
</tr>
<tr>
<td>Multiple regimen failure</td>
<td>Recommended</td>
<td>Recommended</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Sources: HHS panel,51 Hirsch et al,69 David Katzenstein, Richard Haubrich.

For David Katzenstein, the clinical rationale for resistance testing can be distilled to a simple syllogism:

1. GART and other studies show that the number of active drugs in a new regimen determines that regimen’s success.
2. Resistance testing helps identify active drugs.
3. Therefore, resistance testing can improve a regimen’s success.

But because Katzenstein’s role at the IAPAC Sessions 2002 was to dissect the limits of resistance testing, he went ahead and did so—even though he called some of his own criticisms “carping.” He began with perhaps the most vexing resistance riddle:

Susceptibility and resistance evolve along a continuum for any given drug or virus. Researchers, labs, and assay makers propose cutoffs, typically expressed as a fold change in inhibitory concentration. But HIV doesn’t know about cutoffs. So for any resistance readout, the clinician must ask two questions:

1. **How much activity** is enough to warrant inclusion in a new regimen?
2. **How much resistance** is enough to warrant exclusion?

That those questions must be answered suggests science has not yet replaced art in interpreting resistance.

Richard Haubrich called Virco’s biologic cutoffs a big step in improving clinicians’ ability to use resistance testing. Ultimately, though, Haubrich said clinical cutoffs will be needed, that is, cutoffs defined from data that relate resistance assay results to clinical response. Two cutoffs may be needed for each drug—the first defining the inhibitory concentration at which a drug’s antiviral activity begins to wane, and the second marking the point where the drug has no activity. Researchers at GlaxoSmithKline and Gilead proposed clinical cutoffs for abacavir and tenofovir. But both efforts depended on studies that added each drug to a failing regimen. And such studies become less likely as this so-called intensification strategy falls from favor.

Besides defining clinical cutoffs, Katzenstein noted, research must grapple with the still blunted sensitivity of these assays. “We’re in a technologic bind,” he said, in that assays detect resistance only if it affects an ample slice of the viral population. Resistance-conferring mutations must sully more than 20 percent of a viral population before a genotypic assay spots them as a mixture, he estimated. More than 50 percent must have ebbing sensitivity to a drug before phenotyping can figure an accurate 50 percent inhibitory concentration \((IC_{50})\). With the Virtual Phenotype, he said, the 20 percent rule applies because the test actually matches genotypes.

One advantage of the Virtual Phenotype, session chair Daniel Kuritzkes offered, is that Virco constantly updates the genotype database with which a submitted sample is compared. Reports that come with standard genotyping, on the other hand, use rules set...
by experts who meet periodically, so their advice may lag new findings. But Kuritzkes cautioned that Virtual Phenotypes need careful interpretation. The report will tell you, for example, that 85 percent of the database isolates matching the submitted sample’s genotype are susceptible to a certain drug. One way to read this result is that the sample has a 15 percent chance of being resistant to that drug. And when the percent of matching isolates in the database susceptible to a drug becomes 65 percent or 60 percent, he added, “you’re much closer to a coin toss.”

Even when a resistant population is big enough to set off a resistance assay alarm, Katzenstein said, other factors may muddy application of the results. Yes, your patient’s virus may be susceptible to drug Z, but can your patient keep drug Z concentrations at the level needed to stymie replication? Or will shaky adherence, sluggish absorption, or drug interactions yield dangerously low troughs?

Then there are those inky questions of mutational interactions. One could write a fat tract on this issue alone—and solve nothing doing so. Katzenstein offered one example, the 184I or V mutation that makes virus resistant to 3TC. Work by his colleague Nancy Shulman showed that these mutations lowered the IC50 of AZT 9-fold and of d4T 2-fold, while boosting the IC50 of ddI 2-fold and of abacavir 7-fold.

Haubrich tossed in another caveat: Different labs interpret different resistance results differently. He referred to the ENV A-3 study, which sent 132 labs five coded viral samples, asked them to rate drugs as active, partially active, or inactive against the isolates, then asked for an interpretation. For a virus with the 90M mutation, for example, 70 percent of the labs advised that nelfinavir would prove inactive, while 22 percent predicted it would be partially active. For someone with a history of a few PI failures, that call could be important.

And that honest difference in interpretation does not even touch the issue of quality assurance. Plenty of labs, ENV A-3 showed, just make the wrong call, especially when sizing up an isolate that’s part mutant and part wild type. How can you tell whether your lab is up to snuff? Kuritzkes had some practical suggestions: Ask what quality assurance panels the lab participates in, and ask for their last quality assurance scores. Ask what they do to prevent cross-contamination of isolates.

But, for all its complexity, who would do without resistance testing? Haubrich predicted that the utility of both genotyping and phenotyping will improve as interpretation algorithms gain precision. And, despite difficulties in defining clinical cutoffs, he believes large, ongoing efforts to tie genotype and phenotype to virologic outcome will sharpen interpretation of these tests.

**HIV and HCV: so similar and so different**

The IAPAC Sessions 2002 added a new topic this year, one that gains import as people with HIV live longer, as injection drug users continue to become infected worldwide, and as some of the most potent antiretrovirals insulate the liver—the very organ on which their metabolism depends. That topic is the swirling epidemic of HIV coinfection with hepatitis C virus (HCV) or hepatitis B virus (HBV).

Barbara McGovern (New England Medical Center, Boston) quoted estimates that one third of people with HIV infection also carry HCV. The two viruses share a raft of similarities:

- Replication via RNA
- High rates of viral production
- High rates of replication error
- Genetic heterogeneity
- Mechanisms of viral escape
- Better response to drug combinations

But there’s one big difference between HCV infection and HIV—the first can be cured, and the second can’t. Among people in whom treatment renders HCV undetectable for six months, few suffer relapses. The same clearly cannot be said for HIV. Why? McGovern proposed three answers: (1) HCV replicates in hepatocytes, not in the T-cell captains of the immune system favored by HIV. (2) Once therapy controls HCV in the liver, the organ repairs itself faster than anyone had thought possible. But once HIV assaults the immune system, some damage may be lifelong. (3) HIV briskly finds its way into safe havens—so-called viral reservoirs—from which it can’t be fished. No one has tracked down long-lived HCV reservoirs.

HIV complicates the natural history of HCV, and vice versa. For starters, McGovern said, advanced HIV infection can make HCV harder to diagnose. False-positive ELISAs for HCV become much more common at CD4+ counts below 100 cells/mm3. About 91 percent of coinfected people have HCV detectable in blood, compared with 76 percent infected only with the hepatitis virus. In people with HCV infection who then pick up HIV, the HCV load tends to keep climbing. But people carrying only HCV typically reach a viral set point.

HIV treatment also unleashes HCV in coinfected people. Sandro Vento proposed three possible explanations. (1) The immune reconstitution forged by antiretroviral therapy kills HCV-infected hepatocytes. (2) When untreated, HIV and HCV attain some sort of replicative equilibrium. Controlling HIV upsets the balance, fostering faster HCV replication. (3) Antiretrovirals lower endogenous production of interferon, which controls HCV.

The dangerous liaison between these two viruses suggests worse morbidity and mortality in people who harbor both. Some studies endorse that suggestion; others don’t. McGovern and colleagues reviewed causes of 84 deaths in HIV-infected cohorts in 1991, 1996, and 1998-1999. Most people in those groups—55, 75, and 77 percent, respectively—died of illicit drugs, and most had HCV infection. Alcohol abuse rose from 35 percent and 36 percent in 1991 and 1996 to 73 percent in 1998-1999. So several factors weighed on the morbidity and mortality trends McGovern found.

Deaths from end-stage liver disease accounted for 11 percent of all deaths in 1991. That rate inched up to 14 percent in 1996, then exploded to 50 percent in 1998-1999. More than half who died with end-stage liver disease had an undetectable HCV load or a CD4+ count above 200 cells/mm3 within six months of death. But those hopeful harbingers changed in a good portion of the 1998-1999 cohort, one third of whom had to suspend antiretroviral therapy because of liver toxicity.

A chart review of 263 people with HIV alone, 60 with HCV alone, and 166 with both viruses confirmed the burden of coinfection. Fourteen in the coinfected group (8 percent) had compensated liver disease, but nobody in the other two groups did. Researchers counted 19 deaths (11 percent) among coinfected people, 18 (7 percent) in the HIV-only group, and none in the HCV-only group. Of the 19 deaths among people with HIV plus HCV, nine (47 percent) involved liver disease, compared with none of the deaths in the HIV-only group.
But a large retrospective study found low and stable rates of end-stage liver disease in coinfected populations surveyed in 1995 and 1997. And these were huge cohorts—17,000 people in 1995 and 26,000 people in 1997. So McGovern concluded that questions of morbidity and mortality in coinfected people remain open.

Liver fibrosis rates are higher in men, people who drink alcohol, and people who are older when infected with HCV. In coinfected people, fibrosis progression correlates with a CD4+ count below 200 cells/mm³. In that chart review of 63 coinfected people taking a PI and 119 not taking a PI, liver fibrosis scores were significantly higher in the non-PI group (P = 0.03). But McGovern wondered whether PI therapy, averaging only 14 months, had lasted long enough to account for that difference.

Data on how HCV affects HIV disease are also conflicting. McGovern reported. But at least one study suggests that HIV progression is worse in people coinfected with HCV. In a Swiss HIV Cohort Study involving 3,111 people with HIV, including 1,157 coinfected with HCV, researchers independently linked coinfection and active injection drug use with a higher probability of a new AIDS diagnosis or death. Because HCV coinfection also correlated with a lower CD4+ recovery after starting antiretroviral therapy, the Swiss team concluded that “HCV and active intravenous drug use could be important factors in the morbidity and mortality among HIV-1-infected patients, possibly through impaired CD4-cell recovery.”

Although some aspects of HIV/HCV coinfection remain debatable, the US Public Health Service spelled out a few clear management guidelines, outlined by Stuart Ray (Johns Hopkins University School of Medicine, Baltimore):

- HIV-infected people should be screened for HCV by enzyme immunoassay.
- Coinfected people should be advised not to drink alcohol.
- Coinfected people should be screened for hepatitis A virus IgG and hepatitis B core antibody IgG and, if negative, should be vaccinated.
- Liver enzymes should be monitored when antiretroviral therapy begins.
- Coinfected people should be monitored for liver disease and the possible need for treatment.

Ray agreed with Renslow Sherer’s observation that getting people to give up alcohol “could be the greatest contribution” a clinician makes to HIV/HCV management. Session chair Maurizio Bonacini went so far as to muse that complete abstinence may help the liver as much as pegylated interferon (peg-IFN). He asks people beginning HCV therapy to disavow alcohol for six months. If they can’t make that commitment, he said, they are unlikely to follow other advice.

McGovern advised delaying HBV vaccination in HBV-negative people with a CD4+ count below 200 cells/mm³ until antiretrovirals boost the count. But Ray urged attendees to set a vaccination deadline with such people—perhaps six or 12 months after starting antiretrovirals—and then to vaccinate regardless of CD4+ count. Otherwise, he maintained, the temptation to procrastinate could rob these people of whatever benefit they may derive from the HBV vaccine.

Clinicians familiar with the link between high HIV loads and progression to AIDS must realize, Ray stressed, that HCV RNA levels do not predict prognosis of liver disease. Nor do alanine aminotransferase (ALT) elevations. Thus he emphasized the value of liver biopsy in HCV-infected people. By determining the level of fibrosis, biopsy offers the same prognostic vantage that CD4+ counts do for HIV infection. Besides guiding decisions on HCV therapy, a biopsy may also detect other diseases. He cautioned, though, that the liver is not a “well-mixed” organ, so a biopsy can miss fibrosis. To increase the odds that the sample was good, make sure the pathologist could see at least five portal tracts. Ray added that he does not biopsy people with HCV type 2 or 3; he just begins peg-IFN therapy because they respond at much higher rates than people with type 1 HCV. If they don’t respond, he then gets a biopsy to guide further management.

Treating HIV/ HCV coinfection
Interferon-α has both antiviral and immune-modulating effects, and it toggles cell surface protein expression. This long list of potential impacts on HCV infection, Stuart Ray noted, is a loud clue that no one really knows how the drug works. Interferon’s constant companion, ribavirin, doesn’t lighten the HCV load, but it lowers lofty ALTs. In vitro, ribavirin antagonizes nucleosides, especially AZT. But ribavirin does not blunt nucleosides’ anti-HIV effect in people. Indeed, ribavirin may boost the effect of ddI.

When should you treat HCV infection in people with HIV? Ray proposed these guidelines:

- The primary focus of treatment remains HIV disease.
- For people with advanced (stage 3 or 4) liver fibrosis, treat regardless of CD4+ count to prevent end-stage liver disease.
- For people with mild or moderate fibrosis, treat those with stable HIV disease and a CD4+ count above 350 cells/mm³, with the goal of curing HCV infection.
- For people with no or minimal fibrosis, consider observation.
- For people with decompensated liver disease, the time for treatment has passed.

This advice may well change, he added, if more tolerable drugs such as HCV protease inhibitors prove effective. If they do, it may make sense to treat everyone infected with HCV.

Maurizio Bonacini disagreed only with Ray’s last guideline, arguing that some people with decompensated liver disease can tolerate interferon if treatment begins with a low dose—0.5 µg/kg. If that proves tolerable, he doubles the dose. Bonacini believes a trial should be mounted to test interferon in this population.

Ray advised checking the HCV load 12 weeks after treatment starts. A good response is unlikely if HCV RNA has fallen less than 1 log. In that case continued treatment should be weighed against the burden of toxicity and biopsy-predicted disease progression. After 24 weeks of treatment, fewer than 5 percent of people with a still-detectable HCV load will respond. Maintenance therapy might be considered for some people whose HCV RNA remains detectable.

If people responded to standard interferon then suffer a relapse, Ray doesn’t hesitate to try peg-IFN plus ribavirin. The response rate may be higher in relapers than in all peg-IFN candidates, he said, because they’ve already demonstrated a response to interferon. Bonacini estimated a 30 percent response rate to peg-IFN after relapse following a course of standard interferon.

Twenty-four-week results of an ongoing 48-week study appear to confirm the superiority of peg-IFN plus ribavirin over standard interferon in people coinfected with HCV and HIV. Ray cautioned, though, that ACTG 5071 has another 24 weeks to go and that people are on treatment
during the trial. When they stop therapy, some will have relapses.

This multicenter study randomized 134 people to take 180 µg of peg-IFN weekly or standard-dose interferon. Everyone also took ribavirin, starting with 600 mg daily then escalating to 1 g daily. All study participants had abnormal liver histology, including compensated cirrhosis. They could be antiretroviral naïve with a CD4+ count above 300 cells/mm³ or could be taking a stable antiretroviral regimen with a CD4+ count above 100 cells/mm³ and an HIV load below 10,000 copies/mL.

At study entry the groups did not differ in age (44 years for peg-IFN versus 45 years for interferon), median CD4+ count (452 versus 500 cells/mm³), percent with HIV RNA below 500 copies/mL (60 versus 58 percent), or percent taking antiretrovirals (90 versus 87 percent). Nor did the groups differ in HCV load, percent with HCV genotype 1, fibrosis score, or ALT elevations. At treatment week 24, peg-IFN proved virologically superior regardless of HCV genotype (Table 7). Median CD4+ counts fell in both treatment groups, by 83 cells/mm³ in the interferon group and by 137 cells/mm³ in the peg-IFN group. But CD4+ percents rose in both groups. Neither therapy altered control of HIV.

Four factors predicted an HCV load below 60 IU in a multivariate analysis: treatment with peg-IFN (P < 0.0004), Caucasian race (P = 0.016), a Karnofsky performance score of 100 (P = 0.046), and a fibrosis score of 0 to 2 on a scale of 0 to 6 (P = 0.021). People taking peg-IFN had significantly more grade 4 lab abnormalities (17 versus 4, P = 0.0012), but people tolerated both regimens well. Eight in each group dropped out before week 24, a low rate for an interferon/ribavirin trial that may reflect the dose escalation of ribavirin.

<p>| Table 7. Peg-IFN versus standard interferon for HCV in people with HIV |
|-----------------------------|-----------------------------|-----------------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Interferon + ribavirin</th>
<th>Peg-IFN + ribavirin</th>
<th>P</th>
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</thead>
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<tr>
<td>n</td>
<td>67</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Overall HCV RNA &lt;60 IU*</td>
<td>10 (15%)</td>
<td>29 (44%)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Genotype 1 HCV RNA &lt;60 IU†</td>
<td>4 of 52 (8%)</td>
<td>17 of 51 (33%)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Non-1 genotype HCV RNA &lt;60 IU‡</td>
<td>6 of 15 (40%)</td>
<td>12 of 15 (80%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* Intent-to-treat analysis.
† Response with genotype 1 versus non-1, P < 0.0001.
‡ Source: ACTG 5071.

Ray advised trying nonsteroidal anti-inflammatory drugs and fluids for the fevers and aches that accompany interferon therapy, and selective serotonin reuptake inhibitors (SSRIs) for the depression. He starts SSRI therapy along with interferon in people with a history of alcoholism or a personal or family history of depression. In others he starts an SSRI only if they become depressed while taking interferon. Early results of studies of G-CSF for interferon-associated neutropenia and of erythropoietin for ribavirin-induced anemia look promising.

HIV–HBV dynamics and treatment

Like HIV and HCV, HIV and HBV are perilous partners. Session chair Maurizio Bonacini believes HBV worsened HIV mortality as much as HCV did in a cohort he studied for several years. Barbara McGovern listed three signals of the insalubrious liaison between HBV and HIV:

- Chronic HBV infection developed in more people with HIV infection (23 percent) than in those without HIV (4 percent).
- In another study coinfection raised the risk of HBV chronicity to 40 percent.
- Cirrhosis rates were higher in coinfected people than in those only with HBV.

A study of 5,292 gay men grouped by HBV and HIV infection, and selective serotonin reuptake inhibitors (SSRIs) for the depression. He starts SSRI therapy along with interferon in people with a history of alcoholism or a personal or family history of depression. In others he starts an SSRI only if they become depressed while taking interferon. Early results of studies of G-CSF for interferon-associated neutropenia and of erythropoietin for ribavirin-induced anemia look promising.

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- In another study coinfection raised the risk of HBV chronicity to 40 percent.
- Cirrhosis rates were higher in coinfe

Despite the standard 150-mg twice-daily dose should be used in coinfe

DNA responses are similar in HBV-positive and -negative people. HIV clinicians don’t have to be told the problem with lamivudine monotherapy. In one study of 58 people without HIV infection, 39 had resistance-driven virologic breakthroughs after one year of lamivudine at the 100-mg HBV dose.86

Although adefovir did not make the grade as an antiretroviral, it has done well in HBV trials, including studies of HIV-coinfected people with lamivudine-resistant virus. In one study of 35 coinfected people with lamivudine-resistant HBV while taking the nucleoside as an antiretroviral, adding adefovir at 10 mg daily chopped 4.8 log copies of HBV DNA off the viral load after 72 weeks of treatment.87

Fibrosis scores also fell, and no nephrotoxicity emerged. Tenofovir, adefovir’s nucleotide cousin, took 4.6 logs off the HBV DNA load in 12 HBV-positive people with HIV infection.88 The drug worked equally well in people with and without lamivudine-resistant HBV when starting 300 mg of tenofovir daily, and no new mutants emerged.

Ray concluded that the goal of HBV therapy should be DNA suppression, and the means should be peg-IFN or combination

Ray concluded that the goal of HBV therapy should be DNA suppression, and the means should be peg-IFN or combination
antiviral therapy with lamivudine plus adeovir or tenofovir. He recommended delaying therapy, if possible, in people with an ALT less than two times the upper limit of normal, with or without active histology. HBeAg clearance, he explained, is low in people with low ALTs.99

Treatment breaks, and those “magic and tragic” set points

This year’s edition of the IAPAC Sessions 2002 scheduled no debate on treatment interruptions (TIs). But it’s probably impossible to gather clinical researchers and expert clinicians without the topic coming up—especially if one delegate is Project RIGHT’s Franco Lori.

Diane Havlir, referee of the antiretroviral strategy session, put TIs on the table in a brief traversal of controversial issues. She proposed six risks that accompany treatment breaks:

- Primary infection syndrome during the virologic rebound
- Symptomatic HIV disease resulting from loss of immune control
- Worsening cognitive function
- Threatened adherence
- Loss to clinical follow-up
- Transmission of resistant virus

But Havlir did not propose closing the book on TI trials. Though some question whether the every-other-week tactic studied by Mark Dybul99 can work in clinics with typical three-month follow-up visits, Havlir argued that it’s “premature to say we could never get patients” to stick with an every-other-week schedule.

Pablo Tebas noted, however, that even in Dybul’s tightly controlled study of 10 people, two dropped out and another had a virologic breakthrough (later controlled) when he skipped treatment for 10 days instead of seven. Without much mental strain one can imagine how much faster lost follow-ups and breakthroughs might accrue if trying this strategy in the clinic.

Of course most people who take TIs—with or without their physician’s consent—stop drugs for much longer than seven days. So they risk not only a nearly certain viral rebound, but also a steep slide in CD4+ cells. Tebas recalled his own retrospective study of 72 people with undetectable viremia who interrupted treatment for at least 12 weeks.91 They lost an average 16 CD4+ cells/mm3 monthly, and the only factor that predicted their CD4+ loss was how many T cells they gained with treatment. In other words, Tebas explained, most people tended to sink back to their pre-treatment CD4+ nadir. So a CD4+ count of 600 cells/mm3 after successful therapy does not equal a 600-cell count in someone who never took antiretrovirals.

Franco Lori agreed that there’s something “magic and tragic” about CD4 and RNA set points. In his yet-to-be-presented study of 123 people taking continuous therapy or switching off and on monthly, most virologic failures (<200 RNA copies/mL) in the switch group came in those with a CD4+ nadir below 50 cells/mm3. People with low nadirs, Lori elaborated, returned to them when they interrupted treatment. And people with high baseline viral loads quickly rebounded to those pretreatment levels. He read this seeking of the set point as an argument to begin antiretrovirals sooner.

Lori’s study, like Dybul’s, reckoned a significant improvement in total cholesterol in the TI group (P = 0.01). But he did not repeat Dybul’s finding of significantly improved triglycerides.

Kimberly Smith echoed many clinical researchers’ concerns about drug holidays, arguing that, “We’re tinkering around with these people without really knowing what we’re doing.” But more than one clinician delegate maintained that many people now take drug breaks whether their doctors agree or not. Ignoring that reality instead of engaging patients on the question, they said, helps no one.

And covert break-taking tactics can be surprisingly wily. A clinician practicing in a Brooklyn public hospital discovered some people simultaneously testing their virologic control, their clinician’s savvy, and their own luck. They started with a two-day TI before their next checkup. If the RNA assay counted no virions, they pushed the TI to seven days before the next checkup, then to one month, then to two—always with a certain outcome.

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

References and Notes

The IAPAC Drug Guide (July 2002) features 19 monographs, each a profile of anti-retroviral drugs currently used in the clinical management of HIV disease. Listings are alphabetical by brand name within the three major classes of antiretroviral drugs: NNRTIs, PIs, and NRTIs. Recommended dosage, side effect, drug interaction, and pharmacokinetic data are compiled from multiple sources: Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents (US DHHS, February 4, 2002); Physicians' Desk Reference (2002); Medical Management of HIV Infection (Johns Hopkins University, 2001-2002); Overview of Antiretroviral Drugs (HIV InSite.ucsf.edu, 2002); and official labeling (package inserts) approved by the US FDA and/or other regulatory agencies. The IAPAC Drug Guide will exist as a “living document” at www.iapac.org.

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At a glance
Delavirdine is a potent NNRTI. Delavirdine has been studied in both “protease-sparing” and “protease-containing” regimens. Delavirdine is an inhibitor of the cytochrome P450 enzyme system and therefore has the ability to raise blood levels of saquinavir (Fortovase), indinavir (Crixivan), nevirapine (Viracept), ritonavir (Norvir), and amprenavir (Agenerase), which may allow for potential reduction of dosages (e.g., reduce indinavir dose to 600 mg tid as per package insert). Delavirdine’s ability to increase blood levels of these protease inhibitors makes it unique among the NNRTIs. Delavirdine is now available in 200 mg tablets, as well as 100 mg tablets that can be easily dissolved in liquid (avoid grapefruit juice); taking the drug as a liquid suspension actually increases its bioavailability by 20%. Delavirdine may be taken with or without food. The most common side effect seen in patients using delavirdine has been skin rash that usually lasts less than two weeks.

Potential side effects
Rash, headache, nausea, vomiting, diarrhea, fatigue, and pruritus. Severe rash observed in the NNRTI class may be life threatening. Signs may include fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, or general malaise. A patient should stop taking delavirdine and seek immediate medical attention if these symptoms appear.

Potential drug interactions
Do not use simvastatin (Zocor) or lovastatin (Mevacor); suggested alternatives are atorvastatin (Lipitor), fluvastatin (Lescol), and pravastatin (Pravachol). Alternatives should still be used with caution because of potential for liver toxicity. Tefenadine (Seldane), astemizole (Hismanal), midazolam (Versed), and alprazolam (Xanax) should not be used concurrently with delavirdine. Potential toxicity when given with clarithromycin (Biaxin), dapsone, rifabutin (Mycobutin), prednisone (Dornaseal), and alprazolam (Xanax) should not be used concurrently with delavirdine. Potential toxicity when given with clarithromycin (Biaxin), dapsone, rifabutin (Mycobutin), and rifampin are drugs that decrease delavirdine levels. Certain amphetamines and antihypertensives drugs should not be used with delavirdine. Use of cinemidine (Tagamet) and other drugs in that class is not recommended because they may reduce the absorption of delavirdine. Delavirdine increases indinavir, saquinavir, and saquinavir hard gelatin capsule (Invirase) levels. Absorption of delavirdine is decreased with antacids, including didanosine (Videx or didd) because of its antacid buffer, thus patients should take delavirdine one hour apart from these drugs. Prescriber may need to adjust doses of all these drugs accordingly.

Resistance
Monotherapy results in 50- to 500-fold reduction in susceptibility in most patients within eight weeks. The major mutation changes associated with resistance are at codons 180 and 193 of the RT gene. The K103N mutation confers NNRTI class resistance, while virus with Y181C retains in vitro susceptibility to efavirenz (Sustiva). At present, the NNRTIs (efavirenz, nevirapine, Viramune, delavirdine) are highly cross-resistant.

Pharmacokinetics
Delavirdine, unlike other currently available NNRTIs, is an inhibitor rather than inducer of CYP isozymes. Consequently, the drug interaction profile and rationale for combining delavirdine with other antiretroviral agents is unique among the current NNRTIs. Delavirdine inhibits the CYP3A4-mediated metabolism of protease inhibitors and thereby increases system exposure to these drugs.

Recent updates
Amprenavir is an effective inducer of delavirdine metabolism: A steady state pharmacokinetic interaction study between amprenavir and delavirdine in healthy volunteers
The pharmacokinetic interaction between delavirdine (600 mg bid) and amprenavir (600 mg bid) at steady state was studied in 18 healthy male volunteers. The administration of delavirdine increased the median amprenavir C12h from 112 to 252 ng/ml (p = 0.0039) and the median amprenavir AUC(0-12h) from 8737 to 20059 ng/mlh (p = 0.0039). The administration of amprenavir decreased the median delavirdine C12h from 7916 to 933 ng/ml (p = 0.0039) and the median delavirdine AUC(0-12h) from 160609 to 62715 ng/mlh (p = 0.0078). Coadministration of delavirdine and amprenavir is associated with a favorable increase in the amprenavir C12h, but a dramatic decrease in the delavirdine C12h. The administration of delavirdine 600 mg bid and amprenavir 600 mg bid in combination is not recommended.

Lack of hepatotoxicity associated with non-nucleoside reverse transcriptase inhibitors
A retrospective study was performed to determine the incidence of NNRTI hepatotoxicity in a group of 272 patients with HIV infection who were treated with delavirdine (15%), efavirenz (33%), or nevirapine (52%). A total of 18 patients were coinfected with HBV and 24 patients were coinfected with HCV. The overall rate of grade 3 or 4 elevations in ALT or AST was 1.1% and did not differ significantly among the NNRTI treatment groups. Coinfection with HBV or HCV was not associated with a significant increase in ALT or AST elevations. Palomo R, Koo BC, Shoultz DA, Dieterich DT. J Acquir Immune Defic Syndr 2002;29:340-345.

Combination therapy with indinavir, ritonavir, and delavirdine and nucleoside reverse transcriptase inhibitors in patients with HIV/AIDS who have failed multiple antiretroviral combinations
The antiretroviral efficacy of the combination of indinavir, ritonavir, and delavirdine, and two NNRTIs was examined retrospectively in 10 patients with HIV infection who failed at least three different HAART regimens. The median plasma HIV RNA level prior to initiating IDV/RTV/DLV was 359,300 copies/ml. Overall, eight patients experienced a decrease in HIV RNA after switching to IDV/RTV/DLV, and four patients maintained a 1 log copies/ml reduction in HIV RNA for at least six months. The mean CD4+ count increased from 142 to 273 cells/mm³ after switching to IDV/RTV/DLV. Plasma IDV concentrations in three patients were >1,000 ng/ml. In conclusion, a partial antiretroviral response to IDV/RTV/DLV can be achieved in heavily pretreated patients.

A randomized trial of nelfinavir, ritonavir, or delavirdine in combination with saquinavir-SGC and stavudine in treatment-experienced HIV-1-infected patients
The impact of saquinavir-enhancing therapy was determined in 73 patients with HIV infection previously treated with NRTI with or without saquinavir-HSCG. The patients were randomized to one of three groups: Group 1 received nelfinavir, saquinavir-SGC, and stavudine; Group 2 received ritonavir, saquinavir-SGC, and stavudine; Group 3 received delavirdine, saquinavir-SGC, and stavudine. The median baseline viral load and CD4+ count was 3.6 log copies/ml and 370 cells/mm³, respectively. At 24 weeks, the median decreases in plasma viral loads were 0.26, 0.71, and 0.29 in Groups 1, 2, and 3, respectively. The median increases in CD4+ counts at 24 weeks were 52, 40, and 69 cells/mm³ in Groups 1, 2, and 3, respectively. Changes in viral load and CD4+ counts at 24 and 48 weeks were not significantly different between the groups. More patients discontinued treatment due to drug intolerance or toxicity in the ritonavir group (35%) than in the nelfinavir (15%) or delavirdine (5%) groups. Smith D, Hales G, Roth N, et al. HIV Clin Trials 2001;2:193-199.
At a glance
Efavirenz is the only NNRTI to be used in combination regimens as a first-line therapy for treatment-naïve patients. In contrast to nevirapine (Viramune) and delavirdine (Rescriptor), efavirenz appears to be effective in patients with high baseline viral loads (>100,000 copies). Efavirenz has been used successfully in protease inhibitor-sparing regimens. Efavirenz plus Combivir (zidovudine/Retrovir or AZT)/lamivudine (Epivir or STC) demonstrated greater and more durable viral suppression than indinavir (Crixivan) plus Combivir through three years of follow-up. A addition of efavirenz to two NRTIs plus indinavir adds substantially to activity without significant change in tolerability. Efavirenz is metabolized by CYP3A4. Efavirenz increases nefluravir (Viracept) levels. Efavirenz reduces amprenavir (Agenerase), lopinavir (Kaletra), and saquinavir (Fortovase) levels. Women should avoid becoming pregnant while taking efavirenz. Efavirenz is well tolerated. Most patients experience central nervous system (CNS) side effects during the first two weeks of therapy.

Potential side effects
CNS symptoms (eg, depression, dizziness, headache, somnolence, hypotonic trance), psychiatric symptoms (eg, confusion, insomnia, hallucinations, vivid dreams or nightmares, depression, euphoria or mania, agitation), rash, nausea, vomiting, diarrhea, and increased liver enzymes. These symptoms occur early and generally resolve within two to four weeks. In a small number of patients, serious psychiatric symptoms have been reported. Rash is the most common adverse event. Rash is more common, and more severe, in children. Fever and low levels of neutrophils are also more common. Some patients in recovery experience flashbacks. Women should not become pregnant because of the risk of birth defects.

Potential drug interactions
May cause methadone withdrawal. When taken with efavirenz, indinavir should be increased to 1,000 mg q8h. Lopinavir should be increased to four capsules bid. Because saquinavir decreases 60%, it should be avoided. Interactions not including saquinavir/ritonavir — knowledgeably physicians double saquinavir to 800 mg bid. Efavirenz and ritonavir increase when used together and increase risk of liver damage and other potential side effects. Do not take with astemizole (Hismanal), midazolam (Versed), trazodone (Halcion), or ergot medications (in any form — serious interactions seen with dilatation during gynecological exams). Reduces clarithromycin (Biaxin) dose by 37%. May affect warfarin (Coumadin) therapy. Back-up method to the birth control pill is recommended because of potential for fetal deformities.

Resistance
HIV will develop high level resistance to efavirenz when two mutations occur. Resistance mutations at codons K103N, Y188L, and K103N/Y188L are likely to make efavirenz ineffective. K103N is a key resistance mutation for all current NNRTIs. At present, the NNRTIs (efavirenz, nevirapine, delavirdine) are highly cross-resistant. Studies are currently under way to determine whether a higher dose given bid is effective at blocking replication of HIV already resistant to other NNRTIs, particularly nevirapine.

Pharmacokinetics
Peak efavirenz plasma concentrations are achieved at five hours following a single oral dose. At steady state, the mean Cmax, Cmin, and AUC are dose proportional following 200 mg, 400 mg, and 600 mg daily doses. Steady state plasma concentrations are achieved in six to 10 days. Efavirenz is principally metabolized by the cytochrome P450 system and has been shown to induce P450 enzymes, resulting in the induction of its own metabolism. Efavirenz has an elimination half-life of 40 to 55 hours after multiple doses.

Recent updates
Effect of antiretroviral combination therapies including efavirenz on virologic and immunologic response to regimens containing nevirapine or efavirenz in combination with two nucleoside analogs in the Italian Cohort Naive Antiretrovirals (I.Co.N.A.) Study
In a nonrandomized study, the immunologic and virologic responses to combination antiretroviral regimens containing efavirenz or nevirapine were determined in 694 treatment-naïve patients with HIV infection. Virologic failure was defined as the first of two consecutive measurements of HIV RNA >500 copies/ml. The adjusted relative hazard of virologic failure for patients receiving nevirapine, as compared with those receiving efavirenz, was 2.08. Patients receiving efavirenz recovered greater numbers of CD4+ cells than those receiving nevirapine.

Quality of life, emotional status, and adherence of HIV-1-infected patients treated with efavirenz versus protease inhibitor-containing regimens
The impact of efavirenz-containing combination regimens versus PI-containing regimens on quality of life (QOL) was examined in a prospective study of 100 patients with HIV infection in whom initial treatment with a PI-containing regimen failed. Patients were then randomized to start treatment with two NNRTIs plus efavirenz or two NNRTIs plus one or more new PIs. At week four, patients receiving efavirenz reported dizziness (66%), abnormal dreaming (48%), light-headedness (37%), and difficulty sleeping (35%). At 24 weeks, dizziness, abnormal dreaming, light-headedness, difficulty sleeping, and nervousness decreased significantly. At 48 weeks, itching (13%), abnormal dreaming (10%), and nervousness (8%) persisted in the efavirenz group. Patients in the new PI group reported the following findings at week four: light-headedness (8%), dizziness (5%), difficulty sleeping (4%), nervousness (4%), and headaches (3%). At week 48, patients in the new PI group reported the following: difficulty sleeping (4%), nervousness (3%), headaches (3%), and light-headedness (2%). At 48 weeks, QOL and emotional status scores were significantly higher in the efavirenz group than in the new PI group. High levels of treatment adherence were observed in both groups. The proportion of patients with HIV RNA <200 copies/ml was similar in the efavirenz group (78%) and the new PI group (85%) at 48 weeks. CD4+ cell counts were similar in both groups at 48 weeks. Fumaz CR, Tuldra A, Ferrer MJ, et al. J Acquir Immune Defic Syndr 2002;29:244-253.

Virolologic and immunologic response to regimens containing nevirapine or efavirenz in combination with two nucleoside analogs in the Italian Cohort Naive Antiretrovirals (I.Co.N.A.) Study
In a nonrandomized study, the virologic and immunologic responses to combination antiretroviral regimens containing efavirenz or nevirapine were determined in 694 treatment-naïve patients with HIV infection. Virologic failure was defined as the first of two consecutive measurements of HIV RNA >500 copies/ml. The adjusted relative hazard of virologic failure for patients receiving nevirapine, as compared with those receiving efavirenz, was 2.08. Patients receiving efavirenz recovered greater numbers of CD4+ cells than those receiving nevirapine.


Brand name
Sustiva™

Generic name
efavirenz (or EFV)

Class
Non-nucleoside reverse transcriptase inhibitor (NNRTI)

FDA approval
September 17, 1998

Form
• 50 mg capsule
• 100 mg capsule
• 200 mg capsule
• 600 mg tablet (shown)

Recommended dosage
Adult/adolescent – 600 mg PO qd

Pediatric – For children aged 3 years and older, administer PO qd as follows:
200 mg (10-<15 kg);
250 mg (15-<20 kg);
300 mg (20-<25 kg);
350 mg (25-<32.5 kg);
400 mg (32.5-<40 kg);
600 mg (≥40 kg).

Note(s)
May be taken with or without food. Avoid high fat meals.

Pregnancy
Risk cannot be ruled out.

Manufacturer
Bristol-Myers Squibb

Contact
(800) 334-4486
www.sustiva.com
At a glance

Nevirapine and ketoconazole (Nizoral) should not be administered together. Nevirapine reduces indinavir (Crixivan), lopinavir (Kalétra), and saquinavir-hard gel (Invirase) levels. Macrolides increase nevirapine. At one year, nevirapine plus Combivir (zidovudine [Retrovir or AZT]/lamivudine [Epivir or 3TC]) had at least similar efficacy and acceptable tolerance as nelfinavir (Viracept) plus Combivir in HIV-infected naive patients. Preliminary 32-week results in a small group (50 people) suggest equivalency to indinavir, even in people with a high viral load (>100,000), plus greater T-cell increase (223 versus 166). Other preliminary results (24 weeks in 142 patients) suggest equivalency to nefavirin, even in people with >100,000 viral load. Among NNRTIs, there is a high rate of hepatotoxicity, particularly with nevirapine and efavirenz (Sustiva), with high rates of discontinuation; some fulminant hepatic failure cases (including those from nevirapine-containing post-exposure prophylaxis regimens) have resulted in orthotopic liver transplant or death. Nevirapine should be targeted to persons with CD4+ count >200 cells/mm3 and accompanied by liver function monitoring during the first three months of therapy. Once-daily dosing recommendation based on limited clinical data.

Potential side effects

Rash, headache, nausea, vomiting, diarrhea, and fatigue. Abnormal liver function tests, including the development of hepatitis. May need to stop taking nevirapine until liver function returns to normal. Permanently discontinue if abnormalities return. Severe and life-threatening skin reactions and hepatotoxicity, including fatal cases of each, have occurred. Symptoms of severe rash may include fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, or general malaise. Patients who experience these symptoms should stop taking nevirapine and seek immediate medical attention. Do not increase dose if rash develops during dose escalation or if the patient develops any rash accompanied by the above listed conditions. Granulocytopenia is more common in children than in adults.

Potential drug interactions

May cause methadone withdrawal. Nevirapine reduces levels of protease inhibitors and thus these drugs should not be taken at the same time, or the doses must be increased. Indinavir should be increased to 1,000 mg q8h. Lopinavir should be increased to four capsules bid. Nevirapine interacts with rifampin requiring dose adjustment, but not with rifabutin (Mycobutin). The effectiveness of birth control pills may be decreased; use alternative contraception.

Resistance

Monotherapy is associated with rapid and high-level resistance, with primary RT mutations at codons 103 and 181, which increases the IC90 by >100-fold. There is cross-resistance with delavirdine (Rescriptor); cross-resistance with efavirenz is more variable and in vitro it requires the presence of the K103N mutation, which causes cross-resistance to all currently available NNRTIs. There is evidence that administration of nevirapine with zidovudine may predispose to emergence of the K103N mutation. There is no cross-resistance with NRTIs or PIs. When nevirapine is given alone or combined with zidovudine, there is >100-fold reduction in sensitivity to nevirapine within eight weeks.

Pharmacokinetics

Nevirapine is readily absorbed (>90%) after oral administration. Absolute bioavailability is 95% following single-dose administration. Peak plasma nevirapine levels increase linearly in the dosage range of 200 to 400 mg/day following multiple doses. Nevirapine is highly lipophilic and about 60% bound to plasma proteins. Concentrations of nevirapine in cerebrospinal fluid (CSF) are about 45% those in plasma. Nevirapine is an inducer of hepatic cytochrome P450 metabolic enzymes.

Recent updates

Virological, immunological, and clinical impact of switching from protease inhibitors to nevirapine or to efavirenz in patients with human immunodeficiency virus infection and long-lasting viral suppression.

A group of 77 patients with HIV infection and long-standing viral suppression continued PI-based combination therapy or were switched from PI to nevirapine or efavirenz. At 12 months, viral suppression was maintained in 96% of those switched to nevirapine, 92% of those switched to efavirenz, and 92% of those continuing PI. Significant increases in CD4+ counts were observed in all three groups. Lipid profiles improved but GGT and ALT levels increased significantly in the nevirapine group. One patient receiving nevirapine discontinued treatment due to hepatotoxicity. In the efavirenz group, GGT levels increased and three patients discontinued treatment due to hepatotoxicity. Quality of life improved significantly in the nevirapine and efavirenz groups. In patients receiving effective PI-based therapy, the replacement of PI with either nevirapine or efavirenz is safe and virologically effective.


Effect of nevirapine (NVP) for perinatal HIV prevention appears greatest among women with most advanced disease: Subgroup analyses of HIVNET 012

HIVNET 012 was a randomized open label trial in Uganda which demonstrated the overall efficacy of two doses of nevirapine given to HIV-infected mothers at the onset of labor and to their neonates compared with zidovudine administered intrapartum and postpartum. Retrospective subgroup analysis of 583 women enrolled in the trial revealed that vertical HIV transmission rates were lower among women receiving nevirapine than in those receiving zidovudine, and the difference was greatest among women with the highest viral loads and lowest CD4+ cell counts. Among women with HIV RNA 500 to 9,999 copies/mL, the rate of vertical HIV transmission was 12.3% and 6.2% in those receiving zidovudine and lamivudine, respectively. Among women with HIV RNA >50,000 copies/mL, the rates of vertical HIV transmission were 44.6% and 24.9% in those receiving zidovudine and nevirapine, respectively. Among women with CD4+ counts ≤200 cells/mm3, the rate of vertical HIV transmission was 54.9% and 31.6% in those receiving zidovudine and lamivudine, respectively. The findings support the efficacy of the nevirapine two-dose peripartum regimen for the prevention of vertical HIV transmission, even among women with advanced HIV infection.

Fowler MG, Nwaiwuta A, Guay L, et al. 9th Conference on Retroviruses and Opportunistic Infections. February 2002, Seattle. Abs. 120.

Hepatotoxicity associated with nevirapine- or efavirenz-containing antiretroviral therapy: Role of hepatitis C and B infections

The incidence of severe hepatotoxicity (grade 3 or 4 change in ALT or AST) was prospectively determined in 368 patients with HIV infection receiving combination antiretroviral therapy with nevirapine or efavirenz. HCV and HBV infection was detected in 43% and 7.7% of the patients, respectively. Severe hepatotoxicity was detected in 15.6% and 8.0% of those receiving nevirapine and efavirenz, respectively. Overall, 32% of nevirapine-associated and 50% of efavirenz-associated cases of severe hepatotoxicity were detected during the first 12 weeks of treatment. The risk of severe hepatotoxicity was significantly greater among those with chronic viral hepatitis (69% of cases) and those receiving concurrent PPI (82% of cases). However, 84% of those with chronic HCV or HBV infection did not develop severe hepatotoxicity.

At a glance

Amprenavir is usually well tolerated. Side effects include rash, diarrhea, and nausea. No serious adverse events or laboratory tests abnormalities are usually found. Amprenavir is recommended as an alternative for initial treatment of established HIV infection. The usual dose—eight 150 mg (1,200 mg) capsules bid—creates a pill burden issue with regard to adherence. Ritonavir (Norvir) increases amprenavir levels significantly (once-daily dosing with ritonavir is being evaluated). A ritonavir/amprenavir-based regimen has been of value in salvage therapy. The association with lopinavir (Kaletra) dramatically decreases amprenavir plasma concentrations; however, the levels are still well above those obtained with standard amprenavir dosing (1,200 mg bid). The pill burden associated with amprenavir is a major drawback. However, it can be reduced with ritonavir (four amprenavir capsules (600 mg) with one ritonavir capsule (100 mg) twice a day equals the full amprenavir dose).

Potential side effects

Nausea, vomiting, abdominal pain, taste disorders, fatigue, headache, rash, anemia, colitis, bruising easily, prolonged bleeding, depressive or mood disorders, circulatory disturbances (tingling or numbing around the mouth), and peripheral paresthesia. Gaseous symptoms are common and may be severe. Taking amprenavir with food may help, but check for pancreatitis when there is severe stomach pain. Seen with all the other protease inhibitors are high blood levels of cholesterol and triglycerides, and perhaps associated heart disease, lipodystrophy (body fat changes, including thinning of the face, arms, and legs, with or without fat accumulation in the stomach, breasts, and sometimes the upper back), worsening or new cases of diabetes symptoms include increased thirst and hunger, frequent urination, unexplained weight loss, fatigue, and dry itchy skin), and increased bleeding in hemophiliacs.

Potential drug interactions

Do not use simvastatin (Zocor) or lovastatin (Mevacor); suggested alternatives are atorvastatin (Lipitor), fluvastatin (Lescol), and pravastatin (Pravachol). Alternatives should still be used with caution because of potential for liver toxicity. Delavirdine (Rescriptor) and neflavin (Viracept) greatly increase amprenavir blood levels (and usually stomach discomfort) and prescriber may need to adjust dose accordingly. Flavirez (Sustiva) has been shown to significantly reduce blood levels of amprenavir unless also taken with ritonavir mini-dose. Interacts with several antihistamines, sedatives, and antifungal drugs. Do not use with rifampin. Dose reduction of rifabutin (Myambutol) is necessary. Increased blood levels and drug activity are seen with dapsone, erythromycin, itraconazole (Sporanox), alprazolam (Xanax), clarithromycin (Biaxin), diltiazem (Cardene), nifedipine (Procardia or Adalat CC), and nimodipine (Nimotop). Due to the high vitamin E content in amprenavir capsules, close monitoring of patients on anticoagulants, including herbs such as garlic, feverfew, gingko, and gingo biloba, is recommended. Ibuprofen (Advil) can also be problematic. Do not take extra vitamin E. Pro tease inhibitors increase blood levels of sildenafil citrate (Viagra), thus the sildenafil citrate dose should be started at 12.5 mg and increased as needed and tolerated.

Resistance

Although there is evidence of some cross-resistance between amprenavir and the other protease inhibitors, there is also evidence that the ISV mutation is unique to amprenavir. Consequently, people with resistance to the established protease inhibitors may benefit from the use of amprenavir in salvage regimens. However, ISV compromises response to lopinavir. One study found that the number of protease inhibitors previously taken, and the duration of protease inhibitor treatment, did not predict phenotypic resistance to amprenavir. Instead, the B4 mutation and a naturally occurring variation, I5L, were associated with amprenavir resistance. However, another study reported that children with multiple resistance secondary mutations associated with the L90M mutation often responded poorly to amprenavir-based treatment. In contrast, the D30N mutation associated with resistance to neflavin (Viracept) did not reduce the effectiveness of amprenavir. Furthermore, the N88S protease mutation has been associated with increased sensitivity to amprenavir, and HIV that is resistant to amprenavir may still be inhibited by saquinavir (Fortovase), indinavir (Crixivan) or nelfinavir. An in vitro study has shown that HIV develops amprenavir-related mutations, its ability to replicate lessens. This contrasts with the pattern seen with other protease inhibitors, where an increasing number of mutations will restore replicative capacity. This preliminary finding suggests that amprenavir may limit viral rebound and immune system damage in patients with extensive protease inhibitor experience.

Pharmacokinetics

The time to peak concentration (Tmax) of amprenavir in adults is typically one to two hours after a single oral dose. The absolute oral bioavailability of amprenavir has not been established, and the bioavailability of amprenavir oral solution is 14% less than that of the capsules. Increases in the area under the plasma concentration versus time curve (AUC) are dose proportional after three weeks of oral administration of doses from 300 to 1,200 mg bid. The apparent volume of distribution is about 430 L in healthy adults. Amprenavir is metabolized in the liver by the CYP 3A4 enzyme system. The plasma elimination half-life of amprenavir is 7.1 to 10.6 hours. The effect of renal impairment on amprenavir elimination in adults has not been studied.

Recent updates

Emergence of resistance to protease inhibitor amprenavir in human immunodeficiency virus type 1-infected patients; selection of four alternative viral protease genotypes and influence of viral susceptibility to coadministered reverse transcriptase nucleoside inhibitors

Retrospective genotypic and phenotypic resistance analyses were performed on plasma samples obtained from 48 patients with HIV infection who experienced virologic failure during treatment with amprenavir. Paired baseline and on-therapy isolates from 31 patients (65%) demonstrated the selection of protease resistance mutations. These mutations fell into four distinct categories characterized by the presence of either ISV, I50V, I54L, or I54M and V32I+I47V and often included accessory mutations, commonly M46L. The ISV and I54L genotypes were associated with the greatest reductions in susceptibility to amprenavir, and each of the amprenavir-selected genotypes conferred little or no cross-resistance to other PIs. There was a significant association between baseline resistance to nucleoside RTIs received during combination therapy and the development of protease resistance mutations. Maguire M, Shortino D, Klein A, et al. Antimicrob Agents Chemother 2002;46:731-738.

A prospective study of deep salvage therapy with lopinavir/r, amprenavir, and NRTIs: Final 24-week data, pharmacokinetics, and association of drug levels/drug susceptibility with virologic response

A group of 22 patients with HIV infection and virologic failure to all three available antiretroviral drug classes were treated with nucleoside RTIs, lopinavir/ritonavir (400/100 mg bid), and amprenavir (600 mg bid). At entry, median time on HAART was 45 months, median CD4 cell count was 177 cells/mm³, and median viral load was 4.8 log copies/ml. Median decreases in viral load were -1.18 and -1.13 log copies/ml at week 8 and 24, respectively. The mean increase in CD4+ cell count was 88 cells/mm³ at 24 weeks. Of 22 HIV isolates, 14 (64%) showed a mean 3.5-fold resistance to amprenavir and a mean 27.7-fold resistance to lopinavir. Plasma amprenavir levels were lower than those from reference cultures. Higher plasma lopinavir levels at three hours post-dose were independently predictive of the maximal viral load reduction between weeks 2 and 16. Grade 3-4 laboratory adverse events developed in 11 patients (50%), and six patients (27%) discontinued treatment due to adverse events. Baldini F, Rizzo MG, Hoetelmans R, et al. 9th Conference on Retroviruses and Opportunistic Infections. February 2002. Seattle. Abs. 423-W.
At a glance
Indinavir, in combination with NRTIs (eg, zidovudine (Retrovir or AZT) plus lamivudine (Epivir or 3TC)), is recommended as first-line therapy for HIV-infected naïve patients. This regimen has demonstrated a reduction in the AIDS-defining illness or death and prolonged HIV-RNA suppression of up to five years. Urethral obstruction and renal stone with hydronephrosis are adverse events prompting discontinuation of therapy (weeks 160 and 171). Some strains of indinavir-resistant HIV are cross-resistant to ritonavir (Norvir), but not all ritonavir-resistant strains are resistant to indinavir. Indinavir plus saquinavir (Fortovase) combination is antagonistic in vitro and difficult to dose.

Potential side effects
Headache, nausea, and kidney stones, which may lead to more serious problems such as kidney failure. Signs include back pain, fever, abdominal tenderness, and painful urination. Patients should immediately contact their health professional if pain develops in the middle to lower stomach or the back, or if there is blood in the urine. Other potential side effects include hair loss, changed skin color, severe skin reactions (such as hoarsely dry skin), fatigue or weakness, malaise, diarrhea, loss of appetite, ingrown toe nails (often requiring minor surgery), dry mouth, taste changes, and liver toxicity. Increased uric acid indicates kidney damage (symptoms include joint pain and arthritis). Hemolytic anemia is rare but dangerous: watch for unusual fatigue, jaundice, or reddish-brown urine, and monitor red blood cell counts. Watch out for other drugs also associated with this condition (such as Septra and dapsone). Protease inhibitors may cause high blood levels of cholesterol and triglycerides and perhaps associated heart disease, lipodystrophy (body fat changes, including thinning of the face, arms and legs, with or without fat accumulation in the stomach, breasts and sometimes the upper back), worsening or new cases of diabetes (symptoms include increased thirst and hunger, frequent urination, unexplained weight loss, fatigue, and dry itchy skin), and increased bleeding in hemophiliacs.

Potential drug interactions
Do not use simvastatin (Zocor) or lovastatin (Mevacor); suggested alternatives are atorvastatin (Lipitor), fluvastatin (Lescol), and pravastatin (Pravachol). Nevirapin (Viraprex) increases levels of indinavir but doses of both drugs must remain standard. Increase indinavir to 1,000 mg tid when taken with nevirapine (Viramune) or efavirenz (Sustiva). Alcohol consumption may increase risk of stones. Reduce dosage if using ketoconazole (Nizoral) to 600 mg q8h. Patients should not take indinavir with terfenadine (Seldane), astemizole (Hismanal), trazolam (Halcion), midazolam (Versed), ergot medications (in any form — serious interactions seen with dilation during gynecological exams), and rifampin. Protease inhibitors increase blood levels of sildenafil citrate (Viagra), thus sildenafil citrate dose should be started at 12.5 mg and increased as needed and tolerated.

Resistance
Mutations at codons 10, 20, 24, 32, 46, 54, 63, 71, 82, 84, and 90 correlate with reduced in vitro activity. Substitutions at codons 46 and/or 82 are major mutations that predict resistance. At least three mutations are necessary to produce phenotype resistance. Overlap with ritonavir is extensive, so that strains resistant to one are usually resistant to both. The overlap with other PIs is less extensive, but multiple mutations generally imply class resistance.

Pharmacokinetics
Indinavir is rapidly absorbed with a T_max of 0.8 hours. A greater than dose-proportional increase in indinavir plasma concentrations is observed over the 200 to 1,000 mg dose range. At a dosing regimen of 800 mg q8h, steady state AUC was 30,691 nM/hr, C_max was 12,617 nM, and trough was 251 nM. Indinavir is metabolized by the CYP3A4 enzyme system. Less than 20% of indinavir is excreted unchanged in the urine.

Recent updates
Therapeutic drug monitoring of indinavir in HIV-infected patients undergoing HAART
To determine the value of therapeutic drug monitoring in patients receiving indinavir, a retrospective analysis of 501 plasma samples of patients treated with various doses of indinavir was performed. A wide range of plasma indinavir levels was observed both within and between patients. The mean plasma indinavir level in patients receiving 800 mg bid was 3,260 ng/ml. The mean plasma indinavir level at a dose of 800 mg bid in combination with ritonavir was 4,191 ng/ml. There was no significant difference in indinavir plasma levels at doses of 1.6 g/d and 2.4 g/d. Of 130 patients studied, 35 had only suboptimal plasma indinavir levels (<150 ng/ml). There was no significant difference between the number of patients with suboptimal plasma indinavir levels in the various dosage regimens. Langmann P, Zilly M, Weisabrich B, et al. Infection 2002;30:13-16.

Five-year review of maternal-fetal outcomes in patients exposed to indinavir sulfate during pregnancy
A total of 264 reports of indinavir exposure during pregnancy were evaluated, of which 200 were prospective (outcome unknown at the time of initial report) and 64 were retrospective (outcome known at time of initial report). Trimester of earliest exposure included first (192 reports), second (44 reports), and third (10 reports). Of the 200 prospective reports, 149 (74%) had known pregnancy outcomes. 44 (22%) were lost to follow-up, and seven (4%) were pending. Outcomes from prospective reports included 106 live births (including 11 premature births, median gestational age 35 weeks), 29 elective aboritions, 13 spontaneous aboritions, and one late fetal death. There were five congenital abnormalities including two chromosomal abnormalities and three disseimlar malformations. The birth outcomes were comparable to US population-based figures and revealed a spectrum of congenital anomalies with no consistent patterns of affected organ systems or timing of exposure. McGhee K, Shields K, Benson J, et al. 9th Conference on Retroviruses and Opportunistic Infections. February 2002, Seattle. Abs. 797-W.

Steady-state indinavir (Crixivan) pharmacokinetics in cerebrospinal fluid (CSF) and plasma in patients receiving low-dose ritonavir (Norvir) as determined by ultra-sensitive CSF sampling
The steady-state pharmacokinetics of indinavir in CSF and plasma were determined in seven patients with HIV infection receiving low-dose ritonavir (Norvir) as determined by ultra-sensitive CSF sampling. The CSF:plasma concentration ratio for the indinavir AUC, C max, and C 12h was 17.8%, 10.9%, and 64.6%, respectively. Low-dose ritonavir increased the free indinavir AUC in CSF three-fold without affecting the CSF:plasma AUC ratio. Free indinavir levels in CSF exceeded the IC 95 of wild-type HIV at all times in every patient. Low-dose ritonavir enhances indinavir disposition into the CSF primarily by increasing indinavir plasma levels and also perhaps by inhibition of P-glycoprotein. Haas DW, Johnson B, Nicotera J, et al. 9th Conference on Retroviruses and Opportunistic Infections. February 2002, Seattle. Abs. 437-W.

Final analysis of the Triledge induction-maintenance trial: Results at 18 months
In a multicenter trial, 279 patients with HIV infection were randomized as follows: Group 1 received zidovudine, lamivudine, and indinavir; Group 2 received zidovudine and lamivudine; and Group 3 received zidovudine and indinavir. A total of 83 patients experienced virologic failure at 18 months, including 10, 46, and 27 patients in Groups 1, 2, and 3, respectively. Overall, 87% of the patients achieved HIV RNA <500 copies/ml at 18 months with no significant difference between the treatment groups. Patients in Group 1 with virologic failure had a greater tendency to maintain HIV RNA >500 copies/ml beyond the time of virologic failure than did patients in the other groups who experienced failure. These findings confirm the failure of less intensive regimens to maintain viral suppression in patients with HIV RNA >500 copies/ml, although randomization to less intensive regimens was also unsuccessful. Flandre P, Raffi F, Descamps D, et al. AIDS 2002;16:561-568.

Brand name
Crixivan®

Generic name
indinavir (or IDV)

Class
protease inhibitor (PI)

FDA approval
March 14, 1996

Form
• 200 mg capsule
• 333 mg capsule
• 400 mg capsule (shown)

Recommended dosage
Adult/adolescent – 800 mg q8h (separate dosing with ddI by 1 hour); bid only when combined with RTV, NFV, or LPV/RTV

Pediatric – No pediatric labeling.

Note(s)
Must be taken on an empty stomach — 1 hour before or 2 hours after meal — with water (for adequate absorption). ≥40 oz fluid/day are needed to prevent kidney stones.

Pregnancy
Risk cannot be ruled out.

Manufacturer
Merck & Co.

Contact
(800) 850-3430
www.merck.com
At a glance
For purposes of this monograph (and since Invirase and Fortovase are different formulations of saquinavir (SQV)) Invirase will be referred to as either saquinavir hard-gel capsule or SQV-HGC; and Fortovase will be referred to as either saquinavir soft-gel capsule or SQV-SCG.

Saquinavir hard-gel capsule was the first protease inhibitor approved by the US Food and Drug Administration (FDA) on December 6, 1995, for use in combination with nucleoside analogs for the treatment of HIV-infected adults. When using saquinavir as part of a combination antiretroviral regimen, the recommended formulation is saquinavir soft-gel capsules. In rare circumstances, SQV-HGC may be considered if this formulation will be combined with antiretrovirals that significantly inhibit saquinavir’s metabolism. In patients with an undetectable viral load who are taking SQV-HGC, switching to SQV-SCG is recommended. SQV-HGC and SQV-SCG are not bioequivalent and cannot be used interchangeably. Saquinavir at doses less than 600 mg bid are not recommended since lower doses have not shown antiviral activity. When saquinavir is taken without food, concentrations of saquinavir in the blood are substantially reduced and may result in no antiviral activity. HIV isolates with reduced susceptibility to saquinavir have been selected in vitro, although the clinical relevance of phenotypic and genotypic changes associated with saquinavir therapy has not been established.

Potential side effects
The most common adverse events in patients receiving SQV-HGC are diarrhea, abdominal discomfort, and nausea. Other reported adverse events include headache, numbness, dizziness, rash, and musculoskeletal pain. Rare toxicities include allergic reaction, anorexia, chest pain, edema, fatigue, weakness, dehydration, hyperglycemia, weight changes, anemia, anxiety, depression, bronchitis, cough, renal calculus, and urinary tract infection.

Potential drug interactions
SQV-HGC should not be administered concurrently with rifampin, since rifampin decreases saquinavir concentrations by 80%. Rifabutin (Myambutol) reduces saquinavir plasma concentrations by 40%. Other drugs that induce CYP3A4 (e.g., phenobarbital, phenytoin (Dilantin), dexamethasone, carbamazepine) may also reduce saquinavir plasma concentrations. Coadministration of saquinavir and ritonavir (Norvir) increases plasma saquinavir levels 17-fold. Saquinavir levels are increased 5-fold when given in combination with delavirdine (Rescriptor). Coadministration of nevirapine (Viramune) with saquinavir results in a 24% decrease in plasma saquinavir levels. Concurrent use of saquinavir with lovastatin (Mevacor) or simvastatin (Zocor) is not recommended.

Resistance
The most common HIV protease mutations observed in patients receiving combination therapy with saquinavir are L90M and I47A. After 24 weeks of combination therapy, about 12% of patients develop one or both of these mutations. Phenotypic resistance changes were not observed at 24 weeks.

Pharmacokinetics
The absolute bioavailability of saquinavir is only about 4%. The low bioavailability is thought to be due to a combination of incomplete absorption and extensive first-pass metabolism. Administration with a high calorie meal increases the mean saquinavir AUC seven-fold. The effect of food persists for up to two hours. Saquinavir is about 98% bound to plasma proteins. The metabolism of saquinavir is cytochrome P450-mediated with the specific isoenzyme, CYP3A4, responsible for more than 90% of the hepatic metabolism. Systemic clearance of saquinavir is rapid.

Recent updates
Comparative pharmacokinetics and short-term safety of twice-daily (bid) Fortovase/Ritonavir and Invirase/Ritonavir
The comparative pharmacokinetics and short-term safety of saquinavir/ritonavir (1000 mg/100 mg bid) administered as Invirase or Fortovase were examined in 24 healthy volunteers. All subjects received saquinavir as Invirase for two weeks and were then crossed over to Fortovase. At steady state, mean trough concentrations at 12 hours post-dose were significantly higher for Invirase (383 ng/ml) than for Fortovase (237 ng/ml). Gastrointestinal adverse effects occurred more frequently with Fortovase than with Invirase. In conclusion, pharmacokinetic enhancement of Invirase with 100 mg of ritonavir produced plasma concentrations that exceeded those of boosted Fortovase.


The interim analysis of a phase IV randomized, open-label, multi-center trial to evaluate safety and efficacy of indinavir/ritonavir (800/100 mg bid) versus saquinavir/ritonavir (1,000/100 mg bid) in adult HIV-1 infection: MaxCD28 Trial
A group of 337 patients with clinical indications for an RTV-boosted PI regimen were randomized to receive SQV/RTV (1,000/100 mg bid) or IDV/RTV (800/100 mg bid). Use of NRTI/NRTI was determined prior to randomization. At 24 weeks, the proportion of patients with HIV RNA <100 copies/ml was 71% in the SQV/RTV group and 66% in the IDV/RTV group (p = NS). Mean increases in CD4+ counts at 24 weeks were 58 and 49 cells/mm3 in the SQV/RTV and IDV/RTV groups, respectively. The time to increase of >100 CD4+ cells was similar in both groups. No significant differences in serious adverse events were observed between the groups.


Plasma drug levels, genotypic resistance, and virologic response to a nelfinavir plus saquinavir-containing regimen
Plasma drug levels and virologic responses were determined in 62 patients with HIV infection who were switched to salvage regimens including SQV/RTV. At baseline, the HIV RNA was 4.78 log copies/ml and the median number of HIV protease gene mutations was nine. After 24 weeks, 19% of patients had HIV RNA <50 copies/ml. A higher baseline number of HIV protease gene mutations and the L90M mutation were associated with treatment failure. Trough levels of NVP and SQV were two- and five-fold, respectively, greater than those achieved when either drug was used individually. Suboptimal PI levels were associated with a poorer response, but there was no correlation between optimal drug levels and a better response.


Randomized salvage therapy with saquinavir-ritonavir versus saquinavir-nelfinavir for highly protease inhibitor-experienced HIV-infected patients
In a prospective trial, 31 patients with HIV RNA >3 log copies/ml and previous PI exposure were randomized to receive salvage therapy with SQV/RTV (600 mg bid/200 mg bid) or SQV/NFV (600 mg bid/1,000 mg bid) and NRTI. At three months, mean CD4+ counts and HIV RNA levels were 316 cells/mm3 and 3.89 log copies/ml, respectively, in the SQV/RTV group; and 448 cells/mm3 and 3.65 log copies/ml, respectively, in the SQV/NFV group. At six months, HIV RNA stabilization or decrease ≥0.5 log copies/ml were observed in 10 patients in the SQV/RTV group and eight of those in the SQV/NFV group. Virologic success was inversely correlated to baseline viral load at three months and the number of HIV protease mutations at six months. In conclusion, both SQV/RTV and SQV/NFV are useful options in patients with multiple HAART failures.


Brand name
Invirase®

Generic name
saquinavir hard-gel capsule (or SQV-HGC)

Class
protease inhibitor (PI)

FDA approval
December 7, 1995

Form
• 200 mg capsule (shown)

Recommended dosage
Adult/adolescent – 400 mg PO bid with RTV (400 mg PO bid)

Pediatric – No pediatric labeling.

Note(s)
Only recommended in combination with RTV.
Must be taken within 2 hours of meal.

Pregnancy
No evidence of risk in humans.

Manufacturer
Hoffmann-La Roche

Contact
(800) 282-7780
www.rocheusa.com
At a glance

For purposes of this monograph (and since Fortovase and Invirase are different formulations of saquinavir (SQV)), Fortovase will be referred to as either saquinavir soft-gel capsule or SQV-SGC; and Invirase will be referred to as either saquinavir hard-gel capsule or SQV-HGC.

Metabolism by saquinavir is mediated by CYP3A4. Some studies have shown increased saquinavir concentration and improved antiviral activity for saquinavir soft-gel capsule compared to saquinavir hard-gel capsule. Saquinavir in combination with efavirenz (Sustiva) should not be prescribed. Saquinavir appears to be well tolerated. Ritonavir (Norvir) increases saquinavir levels 3-fold or higher. Once-daily dosing of saquinavir with ritonavir is being studied. A saquinavir/ritonavir-based regimen is recommended as initial treatment of established HIV infection. All protease inhibitors could cause metabolic abnormalities, redistribution of body fat, new-onset diabetes, or exacerbation of existing diabetes, hepatotoxicity, and may increase the risk of spontaneous bleeding in patients with hemophilia.

Potential side effects

Diarrhea, nausea, abdominal discomfort or pain, flatulence, indigestion, headache, insomnia, fatigue, and taste alteration. Seen with all protease inhibitors are: high blood levels of cholesterol and triglycerides, and perhaps associated heart disease, lipodystrophy (body fat changes, including thinning of the face, arms and legs, with or without fat accumulation in the stomach, breasts, and sometimes the upper back), worsening or new cases of diabetes symptoms include increased thirst and hunger, frequent urination, unexplained weight loss, fatigue, and dry itchy skin, and increased bleeding in hemophiliacs.

Potential drug interactions

Do not use simvastatin (Zocor) or lovastatin (Mevacor); suggested alternatives are atorvastatin (Lipitor), fluvastatin (Lescol), and pravastatin (Pravachol). Alternatives should still be used with caution because of potential for liver toxicity. Increased blood levels with indinavir (Crixivan), ritonavir (Norvir), and nelfinavir (Viracept). Blood levels decreased significantly by efavirenz, but can be taken together if ritonavir is included. Other drugs that may also reduce saquinavir blood levels are nevirapine (Viramune), carbamazepine (Tegretol), phenobarbital, or phenytoin (Dilantin). Nevirapine can be taken if ritonavir is added. Saquinavir should not be taken with rifampin or rifabutin (Mycobutin). Do not take with triazolam (Halcion), midazolam (Versed), sedatives/hypnotics, ergot derivatives (in any form – serious interactions seen with dilation during gynecologic exams), terfenadine (Seldane), and astemizole (Hismanal). High incidence of severe liver problems when taken with delavirdine (Rescriptor). Protease inhibitors (SQV-SGC) are metabolized by CYP3A4 and are inactivated by CYP2C8, CYP2C9, and CYP2D6. Newer protease inhibitors (NPIs) do not appear to interact with saquinavir. Coadministration of saquinavir with ritonavir increases saquinavir levels up to 3-fold. Combination of saquinavir (SQV) with ritonavir (RTV) is not recommended.

Recent updates

Pilot study of saquinavir-SGC (Fortovase, SQV) 100 mg twice daily and lopinavir/ritonavir (Kalera, LPV/r) in protease inhibitor-experienced HIV+ individuals: Dose escalation and combined normalized inhibitory quotient (dNtQ).

In an open-label study, 28 patients with HIV infection who were P-resistant received SQV-SGC (1,000 mg bid) and LPV/r with NRTI guided by virtual phenotype. Median baseline HIV RNA and CD4+ count was 4.96 log copies/mL and 218 cells/mm3, respectively. Virtual phenotype predicted resistance to SQV in 31% and LPV/r in 42%. At week 12, 65% of patients had HIV RNA <50 copies/mL and CD4+ counts increased by a median of 94 cells/mm3. HIV RNA decline was 2.3 log copies/mL at week 12. Neither drug levels nor virtual phenotype alone correlated with virologic response. Overall, 30% of patients required initial SQV dosage reductions primarily due to GI intolerance, followed by dose escalation. Only three patients discontinued treatment due to adverse events. The combined normalized inhibitory quotient, a measure of C3P45fold changes in resistance relative to a corrected reference trough/cutoff fold change, was predictive of the viral suppression at week 12 for this regimen.


Plasma drug levels, genotypic resistance, and virologic response to a nelfinavir plus saquinavir-containing regimen

In a prospective study, 62 patients with HIV infection were switched to a salvage regimen containing SQV/NVP. The median baseline HIV RNA was 4.78 log copies/mL and the median number of mutations in the HIV protease gene was nine. At 24 weeks, 45% of the patients had >0.5 log decrease in viremia and 19% had HIV RNA <50 copies/mL. Treatment failure was associated with a higher number of mutations in the HIV protease gene (12 versus eight, p = 0.001) and the L90M mutation (36% versus 67%, p = 0.001). Trough levels of SQV and NVP were five and two-fold greater, respectively, than those reached when used alone. Suboptimal PI levels were associated with a poorer response, but there was no correlation between optimal drug levels and a better response. Genotypic resistance predicts the virologic response to a SQV-NVP salvage regimen, and higher than optimal drug levels may be needed to control the replication of P-resistant viruses.


FOCUS Study: Saquinavir QD regimen versus Efavirenz QD regimen

24-week analysis in HIV-infected patients

A group of 159 treatment-naive patients with HIV infection were randomly assigned to receive SQV (1,600 mg qd) and low-dose ritonavir (100 mg qd) or efavirenz (600 mg qd). Both groups received two NRTIs. The mean baseline viral load was 4.78 log copies/mL in the SQV group and 4.72 log copies/mL in the EFV group. The mean baseline viral load was 4.78 log copies/mL in the SQV and EFV groups, respectively. At 24 weeks, HIV RNA <50 copies/mL was achieved in 60% and 80% of those in the SQV and EFV groups, respectively, on intent to treat analysis. Mean increases in CD4+ counts were 166 and 144 cells/mm3 in the SQV and EFV groups, respectively. Both regimens were generally well tolerated. Treatment with SQV/low-dose RTV provides potent HIV suppression, tolerability, and convenient once-daily dosing.

Once-daily versus twice-daily Kaletra (lopinavir/ritonavir) in antiretroviral-naïve HIV+ patients: 48 week follow-up

A group of 38 treatment-naïve persons with HIV infection were randomized to receive lopinavir/ritonavir qd (800/200 mg) or bid (400/100 mg) with d4T/3TC bid. Median baseline viral load and CD4+ count was 4.7 log copies/ml and 264 cells/mm3, respectively. The lopinavir AUC and Cmax were similar with both regimens. At week 48, 74% and 79% of the patients in the qd and bid groups, respectively, achieved HIV RNA <50 copies/ml. No relationship between trough drug levels and antiretroviral activity was observed. Treatment adherence was similar in both groups. The most common drug-related adverse effects were nausea, asthenia, and diarrhea, and these events occurred with similar frequencies in both groups and rarely led to drug discontinuation.


Safety and antiviral activity at 48 weeks of lopinavir/ritonavir plus nevirapine and two nucleoside reverse transcriptase inhibitors in human immunodeficiency virus type 1-infected protease inhibitor-experienced patients

In a randomized study, 70 patients with HIV infection and HIV RNA between 1,000 to 100,000 copies/ml on a first PI-containing regimen substituted the PI with lopinavir/ritonavir (400/100 mg or 400/200 mg) bid. Nevirapine (200 mg bid) was added on day 15, and NRTIs were changed. Mean HIV RNA levels decreased by 1.14 log copies/ml after two weeks of treatment with lopinavir/ritonavir. At week 48, 86% of the patients had HIV RNA <400 copies/ml and 76% had HIV RNA <50 copies/ml. Mean CD4+ counts increased by 125 cells/mm3 at week 48. Three patients discontinued treatment due to drug-related adverse events.


At a glance

Patients may keep the drug at room temperature if used within two months of dispensing. Administration with food enhances overall drug levels. Dosing of didanosine (Videx or ddI) and lopinavir should be separated by at least 2.5 hours. Elevation of cholesterol, triglycerides, and liver enzyme levels have been reported. Clinical trials are ongoing in HIV-infected patients with various levels of prior treatment experience. Lopinavir-based therapy demonstrated antiviral activity in antiretroviral-naïve patients through 144 weeks. The rate of discontinuation of therapy due to side effects is low. No evidence of genotypic resistance to lopinavir was observed in any of the isolates from lopinavir-treated antiretroviral-naïve subjects through week 60.

Potential side effects

Rash, loose stools, diarrhea, nausea, headache, muscle weakness, and increased cholesterol, triglycerides, and AST/ALT. These are not lasting samples, needed for the most accurate results. Seen with all older protease inhibitors (except amprenavir (Agenerase)) are high blood levels of cholesterol, and triglycerides, and perhaps associated heart disease, lipodystrophy (body fat changes, including thinning of the face, arms and legs, with or without fat accumulation in the stomach, breasts, and sometimes the upper back), worsening or new cases of diabetes (symptoms include increased thirst and hunger, frequent urination, unexplained weight loss, fatigue, and dry itchy skin), and increased bleeding in hemophiliacs.

Potential drug interactions

Dosage of methadone may need to be increased when taken with lopinavir. Dose increase to four capsules bid with food recommended when using with efavirenz (Sustiva) or nevirapine (Viramune) in treatment-experienced patients, especially protease inhibitor-experienced patients. May lower levels of zidovudine (Retrovir or AZT) and abacavir (Ziagen). Do not use simvastatin (Zocor) or lovastatin (Mevacor); suggested alternatives are atorvastatin (Lipitor), fluvastatin (Lescol), and pravastatin (Pravachol). Alternatives should still be used with caution because of potential for liver toxicity. Protease inhibitors increase blood levels of sildenafil citrate (Viagra), thus the sildenafil citrate dose should be started at 25 mg (half the normal dose) and increased as needed and tolerated. Phenoxybital, phenytoin (Dilantin and others) or carbamazepine (Tegretol or others) may lower blood levels of lopinavir. Reduces effectiveness of birth control pills; use alternative contraceptive. Oral solution contains alcohol, so do not use with disulfiram (Antabuse) or metronidazole (Flagyl). Do not take with flecainide, propafenone, astemizole (Hismanol), terfenadine (Seldane), rifampin, ergot derivatives (in any form—serious interactions seen with dilation during gynecological exams), St. John’s Wort, pimozide (Orap), midazolam (Versed), and bazedazolam (Halcion). Rifabutin (Mycobutin) dose must be lowered.

Resistance

Major resistance mutations have not been defined. Treatment-naive patients treated with lopinavir rarely acquire HIV resistance by genotypic or phenotypic testing. Resistance usually results from multiple protease inhibitor mutations reflecting prior PI-containing regimens at codons 10, 20, 24, 32, 35, 44, 50, 53, 55, 63, 71, 82, 94, and 90.

Pharmacokinetics

Lopinavir is essentially completely metabolized by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing plasma levels of lopinavir. The administration of lopinavir/ritonavir provides mean steady state lopinavir concentrations 15- to 20-fold higher than those of ritonavir. Following multiple dosing for three to four weeks, a mean lopinavir Cmax of 9.6 mcg/mL is achieved at about four hours after administration. Lopinavir is almost completely bound to plasma proteins, and the absolute bioavailability of lopinavir has not been established. The half-life of lopinavir over a 12-hour dosing interval is five to six hours, and <3% of lopinavir is excreted unchanged in the urine after multiple dosing.
At a glance

The antiretroviral effects of ritonavir and other agents such as NRTIs are additive or synergistic against HIV-1. Ritonavir is metabolized by CYP-450 enzyme system and there is potential for pharmacokinetic interactions. Avoid changing from ritonavir to indinavir (Crixivan) or vice versa for drug failure, since high-level cross-resistance is likely. Ritonavir is commonly used as a protease inhibitor-boostering agent resulting in improved pharmacokinetics and more effective regimens (eg, amprenavir [Agenerase], saquinavir [Fortovase], indinavir, and lopinavir [Kaletra]). Ritonavir-boostered protease inhibitor regimens are associated with significant increases in lipids. There are potential atherogenic implications of such changes.

Potential side effects

Asthenia, nausea, diarrhea, vomiting, tingling/numbness around the mouth, hands or feet, loss of appetite, taste disturbance, headache, dizziness, pancreatitis, and alcohol intolerance. Seen with all protease inhibitors are:

- high blood levels of cholesterol and triglycerides (especially with ritonavir)
- and perhaps associated heart disease, lipoatrophy (body fat changes, including thinning of the face, arms and legs, with or without fat accumulation in the stomach, breasts, and sometimes the upper back), worsening or new cases of diabetes (symptoms include increased thirst and hunger, frequent urination, unexplained weight loss, fatigue, and drychy skin), and increased bleeding in hemophiliacs.

Ritonavir has been shown to increase liver enzymes (AST, ALT, and GGT), muscle enzyme (CKM), and uric acid.

Potential drug interactions

May cause methadone withdrawal. Do not use simvastatin (Zocor) or lovastatin (Mevacor); suggested alternatives are atorvastatin (Lipitor), fluvastatin (Lescol), cerivastatin (Baycol), and pravastatin (Pravachol). Alternatives should still be used with caution because of potential for liver toxicity. Cannot be taken with amiodarone HCl (Cordarone), ergot derivatives (in any form—serious interactions seen with dilution during gynecological exams), triazolam (Halcion), astemizole (Hismanal), pimozide (Orap), quinidine, propafenone HCl (Rythmol), terfenadine (Seldane), flecainide acetate (Tambocor), bepridil HCl (Vascor), and midazolam (Versed). Protease inhibitors increase blood levels of sildenafil citrate (Viagra), thus the sildenafil citrate dose should be started at 12.5 mg and increased as needed and tolerated. One report suggested sildenafil citrate should start at half that when taken on a protease inhibitor. The street drug Estasy is greatly increased by ritonavir, and at least one death has been attributed to the combination. GHB is also dangerous with ritonavir. Tobacco and alcohol may lower blood levels of ritonavir.

Increases clarithromycin (Biaxin) levels by 80%. Rifampin decreases ritonavir levels by 35%. Contains alcohol and greatly hastens intoxication (but should not be enough to trigger relapse). Ritonavir should not be taken with disulfiram (Antabuse) or metronidazole (Flagyl).

Resistance

Phenotypic resistance correlates with mutations on the protease gene at codons 46, 63, 71, 82, and 84. Patients failing monotherapy have multiple mutations at codons 20, 22, 23, 36, 46, 54, 63, 71, 82, 84, and 90. The initial mutation was at codon 82. This was followed by mutations at codons 54, 71, and 36; mutations at codons 84 and 90 occurred late and less frequently.

Pharmacokinetics

The mean Cmax and Ctrough at steady state are 11.2 and 3.7 mcg/mL, respectively. Peak concentrations of ritonavir are achieved at about two hours and four hours after oral dosing under fasting and non-fasting conditions, respectively. The absolute bioavailability of ritonavir has not been determined. Cytochrome P450 3A is the major isof orm involved in ritonavir metabolism. The half-life of ritonavir is about three to five hours, and >98% of the dose is excreted in the feces.

Recent updates

The interim analysis of a phase IV randomized, open-label, multicenter trial to evaluate safety and efficacy of indinavir/ritonavir (800/100 mg bid) versus saquinavir/ritonavir (1,000/100 mg bid) in adult HIV-1 infection: MaxCmin1 Trial

In an open-label, phase IV trial, 317 patients with HIV infection receiving NRTI/NRTI were randomized to add IDV/RTV (800/100 mg bid) or SQV/RTV (1,000/100 mg bid). All patients had clinical indications for receiving an RTV-boosted PI regimen. At 24 weeks, 13% of the patients receiving IDV/RTV and 16% of those receiving SQV/RTV experienced virologic failure. No difference in viral suppression was observed between the groups at 24 weeks. At 24 weeks, the proportion of patients with HIV RNA <100 copies/ml was 66% in the IDV/RTV group and 71% in the SQV/RTV group. The mean increase in CD4+ counts at 24 weeks was 40 and 58 cells/mm³ in the IDV/RTV and SQV/RTV groups, respectively. There were no significant differences between the groups in the number of severe adverse events.


Durability of ritonavir (RTV) plus saquinavir (SQV) dual protease inhibitor therapy in HIV infection: Five-year follow-up

A Kaplan-Meier survival analysis was conducted to determine the long-term durability, tolerability, and safety of RTV/SQV. The analysis was based on data from an ongoing study of RTV/SQV with and without NRTI intensification and follow-up to five years. Of 139 patients with HIV RNA >200 copies/ml at baseline, 120 (89%) experienced virologic response (HIV RNA <200 copies/ml) and 87 (64%) had either no viral rebound or experienced re-suppression after experiencing rebound. At five years, 82% of patients on study had HIV RNA <200 copies/ml and a median CD4+ increase of 381 cells/mm³ from baseline. Median increase in CD4+ count from year four to year five was 54 cells/mm³. Nearly half (48%) of patients on study remain on RTV/SQV alone at year five. Between year four and year five, 26% of patients discontinued, mainly for reasons other than adverse events. The findings suggest that RTV/SQV dual PI therapy with or without NRTI intensification has durable activity through five years.


Direct study: A multicenter, open-label, 24-week pilot study with a 24-week extension to evaluate the safety, tolerability and efficacy of indinavir (IDV)-ritonavir (RTV) 800/100 bid in combination with d4T plus 3TC in HIV-infected individuals (Merck protocol 094)

In an open-label, multicenter, non-comparative trial, 89 patients with HIV infection who were naïve to PI, 3TC, and abacavir received IDV/RTV (800/100 mg bid) with d4T and 3TC. The median baseline HIV RNA and CD4+ count was 5.03 copies/ml and 238 cells/mm³. At week 24, mean changes in HIV RNA and CD4+ counts from baseline were -2.61 log copies/ml and +138 cells/mm³, respectively. The proportion of patients with HIV RNA <50 copies/ml at week 24 was 73% by data as observed analysis. The median time to HIV RNA <50 copies/ml was 20 weeks. Overall, 23 patients (28%) discontinued treatment. Nephrolithiasis occurred in 13 patients (15%), of whom five discontinued. In conclusion, IDV/RTV with 4dT and 3TC has potent antiretroviral activity in PI-, 3TC-, and abacavir-naïve patients at 24 weeks.

At a glance
Nelfinavir is metabolized, in part, by CYP3A. Concomitant administration of nelfinavir and delavirdine (Rescriptor) may affect the pharmacokinetics of both drugs. Nelfinavir is recommended as a first-line therapy in antiretroviral-naive patients. When nelfinavir is used in combination with NRTIs, emergence of HIV variants resistant to nelfinavir is delayed. Data from a study of 92 treatment-experienced patients indicates that nelfinavir used in the correct combination may be a viable option for salvage therapy. Loose stools are a common side effect. Moderate hypertension has also been observed. Nelfinavir has an acceptable tolerance.

Potential side effects
Diarrhea, stomach pain, anemia, nausea, flatulence, and rash. Seen with all protease inhibitors are: high blood levels of cholesterol and triglycerides and, perhaps, associated heart disease. Lipodystrophy (body fat changes, including thinning of the face, arms and legs, with or without fat accumulation in the stomach, breasts, and sometimes the upper back), worsening or new cases of diabetes (symptoms include increased thirst and hunger, frequent urination, unexplained weight loss, fatigue, and dry itchy skin), and increased bleeding in hemophiliacs.

Potential drug interactions
Do not use simvastatin (Zocor) or lovastatin (Mevacor); suggested alternatives are atorvastatin (Lipitor), fluvastatin (Lescol), and pravastatin (Pravachol). Alternatives should still be used with caution because of potential for liver toxicity. Patient should not take nelfinavir with terfenadine (Seldane), astemizole (Hismanal), amiodarone HCl (Cordarene), quindine, ergot medications (in any form—serious interactions seen with dilation during gynecological exams), trizolam (Halcion), or midazolam (Versed). Blood levels of Viracept are reduced by rifampin and may be reduced by phenobarbital, phenytoin (Dilantin), and carbamazepine (Tegretol and others). Saquinavir (Fortovase) levels increase three- to five-fold, indinavir (Crixivan) increases 50%, and ritonavir (Norvir) levels are unchanged. Prescriber may need to adjust doses of any of these drugs accordingly. Protease inhibitors increase blood levels of side-effects (Viagra), thus the sildenafil citrate dose should be started at 12.5 mg and increased as needed and tolerated. Rifabutin (Mycobutin) dose must be decreased when used with nelfinavir. Rifampin and nelfinavir should not be used together. Reduces effectiveness of birth control pills; use alternative contraceptive.

Resistance
Nelfinavir resistance is primarily associated with one key mutation at position D30N on the protease enzyme, as well as mutations at positions B4 and L90M. When nelfinavir and saquinavir are both taken, the L90M mutation is most commonly associated with treatment failure. There is some evidence that HIV that is resistant to nelfinavir may not reproduce very efficiently and may not be as destructive of the immune system as other types of mutant virus. The implications of this data are unclear, although it has been suggested that a CD4 count may continue to rise despite a rebound in HIV that is resistant to nelfinavir.

Pharmacokinetics
The bioavailability of nelfinavir ranges from 20% to 80%, and it increases two- to three-fold when nelfinavir is administered with food. Following multiple dosing of 750 mg of nelfinavir tid, maximum concentration at steady-state was three to four mcg/ml and minimum concentration was one to three mcg/ml. The elimination half-life of nelfinavir ranges from three to five hours. Nelfinavir is primarily metabolized by the liver and excreted in the feces.

Recent updates
Randomized salvage therapy with saquinavir-ritonavir versus saquinavir-nelfinavir for highly protease inhibitor-experienced HIV-infected patients
A group of 31 PI-experienced patients with HIV infection and multiple failures of HAART were randomized to receive nelfinavir-saquinavir (1,000 mg bid + 600 mg bid) or ritonavir-saquinavir (200 mg bid + 600 mg bid). Nucleoside analogs were recycled, and nonnucleoside inhibitors were not permitted. Mean previous duration of PI exposure was 31 months for both groups. On intention-to-treat analysis at six months, HIV RNA stabilization or decrease (≥0.5 log) was observed in eight patients treated with nelfinavir-saquinavir and 10 of those treated with ritonavir-saquinavir. Virologic success at three months was inversely correlated to baseline HIV RNA. In conclusion, the combinations nelfinavir-saquinavir and ritonavir-saquinavir may be useful in patients with multiple HAART failures. Chavanet P, Piroth L, Grappin M, et al. HIV Clin Trials 2001;2:408-412.

Drug resistance mutations in HIV-1-infected subjects during protease inhibitor-containing highly active antiretroviral therapy with nelfinavir or indinavir
In a retrospective study, the Swiss HIV Cohort Study was screened for all PI-naive patients who started HAART with nelfinavir or indinavir, achieved a favorable initial response (HIV RNA <400 copies/ml), and were treated for more than 24 weeks. A total of 41 patients (21 treated with nelfinavir and eight treated with indinavir) experienced subsequent treatment failure and were selected for genotypic analysis. The only primary mutation in the nelfinavir patients was 30N. Isolated or combined A62T and G46L mutations were detected in the indinavir patients. The rate of virologic failure and the frequency of resistance mutations at the time of virologic failure was similar in both groups. Yerly S, Rickenbach M, Popescu M, et al. Antivir Ther 2001;6:185-189.

Randomized, double-blind comparison of two nelfinavir doses plus nucleosides in HIV-infected patients
In a phase III, double-blind, placebo-controlled trial, 297 patients with HIV infection were randomized to receive 750 mg nelfinavir tid, 500 mg of nelfinavir tid, or placebo in combination with zidovudine (200 mg tid) and lamivudine (150 mg bid). On intent-to-treat analysis, 55% of patients receiving 750 mg nelfinavir tid and 30% of those receiving 500 mg nelfinavir tid achieved HIV RNA <50 copies/ml compared with 4% of those receiving placebo at 24 weeks. In patients continuing nelfinavir for another 24 weeks, the proportion achieving HIV RNA <50 copies/ml were 61% and 37% in the 750 mg tid and 500 mg tid arms, respectively (p = 0.004). Adverse events were similar in both nelfinavir groups. In conclusion, nelfinavir was superior to placebo when administered in combination with zidovudine and lamivudine, and the 750 mg tid dose was superior to the 500 mg tid dose. Saag MS, Tebas P, Sension M, et al. AIDS 2001;15:1591-1597.

Sequencing of protease inhibitor therapy: Insights from an analysis of HIV phenotypic resistance in patients failing protease inhibitors
The phenotypic patterns of HIV-1 susceptibility to PI were determined in 88 HIV-infected patients who achieved an initial therapeutic response (HIV RNA <400 copies/ml) to multibar drug treatment including nelfinavir (55 patients), indinavir (42 patients), or another PI (11 patients) followed by treatment failure after six months. Decreased susceptibility was defined as ≥2.5-fold increase in the 50% inhibitory concentration compared with drug sensitive control virus. HIV-1 isolates from patients receiving nelfinavir were less likely to have reduced susceptibility to other PIs than isolates from patients receiving indinavir or other PIs, even after adjustment for the duration of prior PI use. Reduced susceptibility to saquinavir and amprenavir was observed less frequently than for other PIs. In conclusion, the frequency of PI cross-resistance and the magnitude of changes in susceptibility varied according to the initial PI used in the failing treatment regimen. Significantly less PI cross-resistance was observed in HIV-1 isolates from patients failing a nelfinavir-containing regimen compared with those from patients receiving other PIs. Kemper GA, Witt MD, Keiser PH, et al. AIDS 2001;15:609-615.
At a glance
Combivir® combines lamivudine (Epivir or 3TC) and zidovudine (Retrovir or AZT), which together exhibit synergistic antiretroviral activity. In patients receiving combination therapy, mutations associated with zidovudine resistance develop more slowly and mutations associated with lamivudine resistance appear to develop rapidly. Co-administration of other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine. Lamivudine plus zidovudine combination is recommended as part of a first-line regimen. Combivir has been shown to be effective as part of protease inhibitor- and NNRTI-based regimens.

Potential side effects
See lamivudine and zidovudine.

Potential drug interactions
See lamivudine and zidovudine.

Resistance
See lamivudine and zidovudine.

Pharmacokinetics
See lamivudine and zidovudine.

Recent updates
CHARM: A phase III open-label, randomized, multi-center study to evaluate the efficacy and tolerability of adding nevirapine and/or hydroxyurea (HU) to a triple nucleoside-based antiretroviral drug regimen in treatment-naive HIV-1-infected subjects
A group of 229 treatment-naive adults with HIV infection were randomized to receive Combivir and abacavir with or without nevirapine (Viramune) or hydroxyurea or prednisolone. Baseline CD4+ counts and viral load were 269 cells/mm³ and 4.6 log copies/ml, respectively. The primary study endpoint was treatment failure, defined as HIV RNA ≥50 copies/ml at 48 weeks. On intent-to-treat analysis, treatment failure was observed in 60.0% and 62.3% of those with and without nevirapine, respectively (p = 0.086), 69.3% and 53.9% of those with and without hydroxyurea, respectively (p = 0.017), and 65.2% and 57.9% of those with and without prednisolone, respectively (p = 0.256). The median time to plasma HIV RNA <50 copies/ml was 91 and 168 days in the patients with and without nevirapine, respectively. A slower increase in CD4+ cell counts was observed in patients receiving hydroxyurea as compared with those not receiving hydroxyurea. Significantly more hypersensitivity reactions were observed in the patients receiving nevirapine.

Treatment intensification with abacavir in HIV-infected patients with at least 12 weeks previous lamivudine/zidovudine treatment
A group of 75 treatment-naive patients with HIV infection were treated with lamivudine/zidovudine or Combivir. At 12 weeks, both treatments were associated with equivalent reductions in HIV RNA, and an identical proportion of patients in each group (74%) demonstrated the M184V mutation. A total of 52 patients with the M184V mutation received treatment intensification with abacavir. The addition of abacavir to Combivir led to further decreases in HIV RNA and increases in CD4+ cell counts at 48 weeks. Multi-nucleotide resistance mutations at codons 69 and 151 were not detected in any patients after 48 weeks of triple combination therapy. All treatment regimens were generally well tolerated. The addition of abacavir to Combivir is a safe and effective therapeutic option and the combination is appropriate for use in patients with the M184V mutation.
At a glance

The majority of lamivudine is eliminated unchanged in urine. Co-administration of lamivudine and zidovudine results in an increase in Cmax of zidovudine. Lamivudine may reverse resistance to zidovudine in zidovudine-experienced patients (hypersensitivity). Co-administration of lamivudine and trimethoprim/sulfamethoxazole (TMP/SMX) results in an increase in lamivudine AUC. Lamivudine as a once-daily component of a triple combination has shown virological efficacy and safety. Lamivudine appears to be well tolerated. Paresthesia and peripheral neuropathies, pancreatitis, lactic acidosis and severe hepatomegaly with steatosis (including fatal cases), have been reported. Lamivudine has been approved for the treatment of hepatitis B virus (HBV) infection.

Potential side effects

Lamivudine is generally well tolerated. However, headache, nausea, diarrhea, fatigue, hair loss, insomnia, malaise, nasal symptoms, cough, and peripheral neuropathy. In children, may cause pancreatitis. Children should be monitored carefully for this condition. Symptoms include nausea, vomiting, clammy skin, and stomach pain that often extends to the back, along with increased amylase in the blood. Rare but potentially fatal toxicity with NRTIs merits special warning: pancreatitis, lactic acidosis, and hepatic steatosis.

Potential drug interactions

TMP/SMX has been shown to increase lamivudine exposure. The use of lamivudine in combination with zalcitabine (Hivid or ddC) is not recommended.

Resistance

HIV can rapidly develop resistance to lamivudine if viral load is not suppressed below the limit of detection of the viral load test. Resistance to lamivudine may also develop when a patient takes a “drug holiday” or treatment interruption, due to the slow decline of lamivudine levels within cells. The mutation associated with lamivudine resistance occurs at codon 184 of the reverse transcriptase enzyme. Despite the common development of the 184 mutation, many patients continue to benefit from combinations that include lamivudine. One possible explanation is that lamivudine-resistant HIV may be less harmful in the body; another possibility is that lamivudine resistance reduces the risk of zidovudine resistance. A third theory is that lamivudine-resistant HIV is less able to mutate again to become resistant to other drugs. HIV that has developed resistance to lamivudine may be cross-resistant to didanosine and zalcitabine; in practice this cross-resistance appears to be rare. Furthermore, moderate resistance to lamivudine may develop in the absence of the 184 mutation if zidovudine-associated mutations are present.

Pharmacokinetics

The absolute bioavailability of lamivudine tablets following oral administration is 86%. The AUC of lamivudine is dose-proportional over the therapeutic range of 0.25 to 10 mg/kg. The apparent volume of distribution of lamivudine following IV administration is 1.3 L/kg, suggesting that lamivudine distributes into extravascular spaces. Binding of lamivudine to human plasma proteins is low (<36%), and the majority of lamivudine is excreted unchanged in urine. The mean elimination half-life of lamivudine ranges from five to seven hours.

Recent updates

Hepatitis B virus and HIV co-infection: Development of lamivudine resistance

In patients co-infected with HBV/HIV, resistance to 3TC develops at a rate of 20% annually. The emergence of 3TC resistance was characterized in a cohort of 47 patients with HBV/HIV co-infection. Of the 29 patients (62%) with HBV replication during treatment with 3TC, only 13 (45%) had HBV polymerase gene mutations characteristic of 3TC resistance. Several combinations of polymerase gene resistance patterns were identified, including M204V + L180M (eight patients), M204I (one patient), M204I + L180M (three patients), and M204I + L215W (one patient). Precore mutations (G1896A) were observed in two patients with 3TC resistance. Patients with 3TC resistance had higher median CD4+ cell counts, CD4+ radii, and HBV viral loads than did patients without resistance. Risk factors for 3TC resistance could not be identified although the majority of patients (72%) with HBV genotype D developed resistance. One-third of patients with 3TC resistance were viremic with wild-type HBV polymerase, and these patients had advanced HIV infection and low median CD4+ cell counts.


Incidence of acute hepatitis B (HBV) infection in HIV-infected persons and the impact of HBV vaccination and lamivudine

The impact of treatment with 3TC on the rate of acute HBV infection was examined in a cohort of participants in the Adult/Adolescent Spectrum of Disease Project, a longitudinal medical record review project. During the 30-month study period, 113 cases of acute HBV infection were diagnosed among 13,012 persons followed for 14,884 person-years (incidence rate, 7.6 cases/1,000 person-years). The adjusted incidence of acute HBV infection was higher in women and in those with a history of alcohol abuse or injection drug use. Only 14% of the cohort received > one dose of HBV vaccine. The relative risk of acute HBV infection was 0.49 in persons receiving antiretroviral therapy with 3TC during three or more six-month intervals as compared with those not receiving antiretroviral treatment.


A randomized trial comparing two four-drug antiretroviral regimens with a three-drug regimen in advanced HIV disease

In phase III open-label study (ACTG 388) 517 treatment-naïve patients with HIV infection were randomized to receive treatment with 3TC and zidovudine and concurrent indinavir (Group 1), efavirenz + indinavir (Group 2), or nelfinavir + indinavir (Group 3). The mean baseline HIV RNA and CD4+ count was 5.42 log copies/ml and 161 cells/mm³, respectively. The median follow-up was 2.1 years. At week 24, the probability of therapeutic response (HIV RNA <200 copies/ml) was 86%, 87%, and 78% in Groups 1, 2, and 3, respectively. CD4+ cell counts increased in all three groups. Among responders, there was lower rate of relapse in group 2 (p = 0.009) and no significant difference in Group 3 compared with group 1 (p = 0.33). There were no significant differences in the incidence of serious adverse events between Groups 1 and 2 and a small increase in Group 3. In conclusion, treatment with 3TC, zidovudine, efavirenz, and indinavir is well tolerated and associated with a superior virologic response. In contrast, treatment with 3TC, zidovudine, nelfinavir, and indinavir results in an inferior virologic response and a greater risk of toxicity compared with the three-drug regimen.


Concentration-controlled compared with conventional antiretroviral therapy for HIV infection

The strategy of a concentration-controlled (CC) approach to combination antiretroviral therapy was compared with conventional fixed-dose (FD) therapy in 40 treatment-naïve patients with HIV infection. The patients were randomized to open-label treatment with lamivudine, zidovudine, and indinavir administered on a CC or FD basis. In the CC group, doses were adjusted to achieve plasma levels of target values. Significantly more patients in the CC group (94%) than in the FD group (53%) achieved HIV RNA levels ≤50 copies at 52 weeks. There were no differences between the groups in the occurrences of laboratory abnormalities or drug-related adverse events.

At a glance
The enteric-coated (EC) formulation consists of small beads coated with a methyl cellulose-based product that permits the drug to pass through the stomach and to be released in the upper portion of the small intestine. The enteric-coated formulation does not include buffering agents (less gastrointestinal side effects). Didanosine EC capsules dosed once daily provide antiviral activity in a triple regimen similar to a reference triple regimen in treatment-naive, HIV-infected subjects.

Potential side effects
Retinal changes, optic neuritis and peripheral neuropathy (tingling, burning, numbness or pain in the hands or feet, indicating nerve damage that is reversible but can be painful and permanently debilitating if not treated in time). Periodic retinal examination recommended. Headache, increased uric acid levels (indicating a number of disorders, including kidney damage and metabolic diseases), and insomnia are other potential side effects. Patients with a history of peripheral neuropathy, pancreatitis, and heavy alcohol use should avoid didanosine. Pancreatitis can be life-threatening and is indicated by increased amylase and lipase levels in lab reports and pain in the stomach and back, along with nausea, vomiting and blood in the urine. Risk increases with higher doses, advanced HIV, and alcohol use. Didanosine enteric-coated capsules may lower risk of gastrointestinal side effects. Rare but potentially fatal toxicity with NRTIs merits special warning: pancreatitis, lactic acidosis, and hepatic steatosis.

Potential drug interactions
Drugs requiring gastric acidity for absorption should be given one to two hours before or after didanosine if the buffered formulation is prescribed. These include capsope, indinavir (Crixivan), ritonavir (Norvir), delavirdine (Rescriptor), ketoconazole (Nizoral), tetracyclines, and fluoroquinolones. Note that this limitation does not apply to nelfinavir (Viracept), amprenavir (Agenerase), saquinavir (Fortovase), efavirenz (Sustiva), or nevirapine (Viramune) and it does not apply when using the enteric-coated didanosine formulation. Alcohol, ganoclass C (Tovenol and Vlaxen), and hydroxyurea (Hydrea) may increase risk of pancreatitis. Methotrexate reduces AUC by 41%. This applies to the didanosine buffered formulation. Consider didanosine dose increase or conversion to non-tablet formulation when using didanosine in a patient taking methotrexate. Didanosine/ stavudine (Hivid or ddc) combination is contraindicated.

Resistance
Mutations at codon 74 are most common; less common are codons 65 and 184. The 184 mutation confers high-level resistance to lamivudine (Epivir or 3TC). From 5% to 10% of patients on didanosine/zidovudine develop mutations that confer resistance to all NRTIs; some are due to T69-SSS insertions and others to the Q151M complex.

Pharmacokinetics
Didanosine is rapidly absorbed, with peak plasma concentrations generally observed within 0.25 to 1.50 hours of oral administration. Increases in plasma didanosine levels are dose-proportional over the range of 50 to 400 mg. The pharmacokinetic properties of standard didanosine in adults include oral bioavailability of 42%, elimination half-life of 1.5 hours, apparent volume of distribution 1.08 L/kg, and systemic clearance rate of 13.0 ml/min/kg. The AUC is equivalent for didanosine-EC and the standard didanosine buffered formulation. The peak plasma concentration of didanosine-EC is reduced about 40% relative to didanosine buffered tablets, and the time to peak concentration increases from about 0.67 hours for didanosine buffered tablets to two hours for didanosine-EC.

Recent updates
Long-term evaluation (25 months) of ddI, 3TC, and efavirenz once-daily regimen in naive patients in Senegal: ANRS 12-04/IMEA 011 Study
In a multicenter trial in Senegal, 40 patients with HIV infection were treated with ddI (400 mg/day), 3TC (300 mg) and efavirenz (600 mg) taken qd at bedtime. Mean baseline HIV RNA was 5.4 log copies/ml and mean baseline CD4+ count was 164 cells/mm3. At 15 months, the mean decrease in HIV RNA was 3.4 log copies/ml and the mean increase in CD4+ counts was 199 cells/mm3. Plasma HIV RNA <50 log copies/ml was achieved by 69% of patients at 15 months. The treatment was well tolerated and 12 grade 3 or 4 adverse events were observed. The findings indicate the long-term efficacy of a simple once-daily HAART regimen in patients with advanced HIV infection and high viral load.


Efficacy and safety of stavudine plus didanosine in asymptomatic HIV-infected children with plasma HIV RNA below 50,000 copies per milliliter
A group of 16 treatment-naive children with asymptomatic HIV infection were treated with ddI (300 mg/m2/day) and stavudine (2 mg/kg/day). At baseline, the mean viral load was 4.05 log copies/ml and the mean CD4+ count was 864 cells/mm3. Plasma viral load <400 copies/ml was achieved by 43% and 44% of the children at 24 and 48 weeks, respectively. The z score for absolute and percentage CD4+ cell counts increased significantly at 48 weeks (+0.63 and +0.97, respectively) relative to baseline. Minor adverse events occurred in 10 children, none of which led to treatment discontinuation. Resistance mutations linked to ddI (L74V or M354V) or 3TC (V75I) were not observed although four children developed ZDV-related mutations T215Y and/or M41I. Lipodystrophy was not observed in any of the participants.


Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medications
The case histories of two HIV-positive women in the third trimester of pregnancy who presented with acute lactic acidosis and acute pancreatitis, respectively, are described. Both women had been on stable antiretroviral regimens containing ddI and 3TC for at least two years before their acute presentations. One case was fatal for the mother and baby. Increased vigilance of pregnant women with HIV infection receiving antiretroviral medications is recommended, particularly during the last trimester of pregnancy.


Virological and immunological response to a once-a-day anti-retroviral regimen with didanosine, lamivudine and efavirenz
In a 48-week pilot study, 75 treatment-naive patients with HIV infection were treated with once-daily ddI, 3TC, and efavirenz. At 48 weeks, the median decrease in HIV RNA was 3.4 log10 copies/ml, and the proportion of patients achieving viral load <50 copies/ml was 77% on intention-to-treat analysis. The mean CD4+ count increased from 251 to 459 cells/mm3 at 48 weeks. Antiviral efficacy was similar in patients with baseline HIV RNA above or below 100,000 copies/ml. The virologic response was significantly worse in patients with baseline CD4+ counts <200 cells/mm3 than those with higher counts. Overall, eight patients discontinued treatment due to adverse effects. The once-daily combination of ddI, 3TC, and efavirenz was well accepted and provided sustained viral suppression in this population.

Brand name
Ziagen®

Generic name
abacavir (or ABC)

Class
nucleoside reverse transcriptase inhibitor (NRTI)

FDA approval
December 17, 1998

Form
• 300 mg tablet (shown)
• 20 mg/mL oral solution

Recommended dosage
Adult/adolescent – 300 mg PO bid; or with 3TC and ZDV as Trizivir 1 tablet bid
Pediatric – For children aged 3 months to 16 years, the recommended dose is 8 mg/kg bid.

Note(s)
May be taken with or without food.

Pregnancy
Risk cannot be ruled out.

Manufacturer
GlaxoSmithKline

Contact
(800) 513-3028
www.gsk.com

At a glance
Abacavir is a prodrug that is pharmacologically active only after conversion to carbovir triphosphate. Abacavir differs from other NRTIs in that it is a carbocyclic nucleoside rather than a dideoxynucleoside. Cross-resistance between abacavir and other NRTIs has been reported. Abacavir increases plasma concentrations of amprapavir (Agenerase), dosage adjustment not required. At 48 weeks, abacavir/lamivudine (Epivir or 3TC) and amprapavir (twice daily) showed to be potent and well tolerated in therapy-naïve patients. Abacavir is generally well tolerated. Potentially life-threatening hypersensitivity reactions (usually within the first six weeks of treatment) have been reported in 5% of clinical trial patients in combination with lamivudine and zidovudine (Retrovir or AZT). Resolves within two days after discontinuation. Do not rechallenge. Lactic acidosis, hepatomegaly with steatosis, and pancreatitis have also been reported. Abacavir has the potential to cross the blood-brain barrier, which may prevent or treat neurological damage (such as dementia).

Potential side effects
Hypersensitivity (allergic reaction) can be fatal. Patients experiencing hypersensitivity must stop taking abacavir and cannot take it again (called "rechallenging"), because of life threatening—and in at least three cases, fatal—reactions. Hypersensitivity usually occurs within six weeks of starting therapy, gets progressively worse, and resolves quickly after permanent discontinuation. Approximately 5% of patients taking abacavir experienced hypersensitivity during clinical trials. The primary symptom is low-grade fever with multi-organ symptoms: muscle ache, nausea, vomiting or other gastrointestinal upset (including abdominal pain), malaise, respiratory symptoms (cough, difficulty breathing, and sore throat), and possibly mild rash. Hypersensitivity might be confused with flu. GlaxoSmithKline recommends that patients with symptoms of acute respiratory disease consider hypersensitivity even if other diagnosis such as pneumonia, bronchitis, or flu is possible. If hypersensitivity is suspected, it is preferable for the patient to immediately contact his/her physician, or be evaluated by a medical provider before discontinuing abacavir. If the patient is unable to talk to or be examined by a medical provider, and the symptoms have worsened with each successive dose of abacavir, the patient may then discontinue abacavir. Black box warning strengthened in 2001 when hypersensitivity was not recognized and patients were re-started on abacavir, becoming seriously ill. Other potential side effects include nausea, vomiting, diarrhea, fatigue, headache, fever, rash, anorexia, high blood sugar, and high triglyceride levels. Rare but potentially fatal toxicity with NRTIs merits special warning: pancreatitis, lactic acidosis, and hepatic steatosis.

Potential drug interactions
Alcohol increases abacavir levels and might increase its side effects. The interaction between alcohol and abacavir was studied in 24 HIV-positive patients. A significant interaction was observed. Females have not been studied.

Pharmacokinetics
Steady state plasma abacavir concentrations are achieved after four weeks of monotherapy. At steady state, the pharmacokinetics of abacavir (area under the plasma concentration-time curve [AUC] and peak concentration $C_{max}$) are dose-proportional over the 100 to 600 mg bid dose range following the administration of multiple doses. Co-administration of zidovudine with abacavir produces a small and inconsistent effect on abacavir pharmacokinetic parameters. At the clinical abacavir dose (300 mg bid), zidovudine has no effect on the abacavir AUC. Zidovudine pharmacokinetics appear to be unaffected by abacavir. The incidence of nausea is significantly associated with the abacavir AUC and $C_{max}$.

Recent updates
Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse transcriptase inhibitor abacavir
MHC allele typing was performed in 200 patients with HIV infection exposed to abacavir. Definite abacavir hypersensitivity was identified in 18 patients, and 15 patients experienced some symptoms but did not meet criteria for abacavir hypersensitivity. HLA-B*5701 was present in 14 (78%) of the 18 patients with abacavir hypersensitivity and in four (2%) of the abacavir tolerant patients. The HLA-DR7/HLA-DQ3 combination was found in 13 (72%) hypersensitive and five (3%) tolerant patients. HLA-B*5701, HLA-DR7, and HLA-DQ3 were present in combination in 13 (72%) hypersensitive and none of the tolerant patients. Other MHC markers also present on the 57.1 ancestral haplotype to which the three identified markers belong confirmed the presence of haplotype-specific linkage disequilibrium and mapped potential susceptibility loci to a region bounded by CA46 and HLA-C. Within the entire abacavir-exposed cohort, the presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 had a positive predictive value for hypersensitivity of 100% and a negative predictive value of 97%. Withholding abacavir in those with HLA-B*5701, HLA-DR7, and HLA-DQ3 should reduce the prevalence of hypersensitivity without inappropriately denying abacavir to any patient. Mallal S, Nolan D, Witt C, et al. Lancet 2002;359:727-732.

Simplification with abacavir-based triple nucleoside therapy versus continued protease inhibitor-based highly active antiretroviral therapy in HIV-1-infected patients with undetectable plasma HIV-1 RNA
In an open-label, multicenter study, 211 patients with HIV infection and a history of undetectable HIV RNA during at least six months of treatment with two nucleoside RTIs and one PI were randomly assigned to replace the PI with abacavir ($n = 105$) or continue the same treatment ($n = 106$). All patients had HIV RNA <50 copies/ml at randomization. A significantly longer time to treatment failure was observed in the abacavir arm as compared with the PI arm, and treatment failure was experienced by a significantly greater proportion of patients in the PI arm (23%) than in the abacavir arm (12%) ($p = 0.03$). Treatment-limiting toxicity occurred in eight patients in the abacavir arm and 14 patients in the PI arm. Significant reductions in plasma cholesterol and triglyceride levels were observed in the abacavir arm at 48 weeks. The number of patients reporting no difficulty in taking their therapy increased significantly from baseline in the abacavir group. Clumeck N, Goebl F, Rozenbaum W, et al. AIDS 2001;15:1517-1526.
At a glance

The antiviral activity of zalcitabine depends on its intracellular conversion to ddCTP. Zidovudine-resistant strains are still susceptible to zalcitabine and vice versa. Concomitant use of zidovudine and zalcitabine against HIV appears to be synergistic. Current recommendations generally advise a three-drug combination including a protease inhibitor, as a second line therapy. Zalcitabine caused peripheral neuropathy in 17% to 31% of trial participants. Zalcitabine and didanosine (Videx or ddI) should not be combined due to increased risk of peripheral neuropathy. Rash, pharyngitis, oral and esophageal ulcers, flu-like symptoms, pancreatitis (potentially fatal), lactic acidosis, and hepatomegaly with steatosis have been observed.

Potential side effects

Headache, fever, skin eruptions, canker sores, general inflammation of the mouth, nausea, pancreatitis, malaise, and peripheral neuropathy. Rare but potentially fatal toxicity with NRTIs merits special warning: pancreatitis, lactic acidosis, and hepatic steatosis.

Potential drug interactions

Due to increased risks associated with peripheral neuropathy, whenever possible zalcitabine should not be taken with NRTIs, amphotericin B (Fungizone), chloramphenicol (Chloromycetin), dapsone, disulfiram (Antabuse), foscarnet (Foscavir), isoniazid (Laniaid or Hydrazid), phenytoin (Dilantin), and probenecid (Benemid). Antacids decrease zalcitabine levels by 25%. Cimetidine (Tagamet), Malaax, foscarnet, and probenecid may decrease zalcitabine levels. When used with zalcitabine, pentamidine (NeoPent or Pentam) may increase risk of pancreatitis. Increased amylase and lipase levels in lab reports and pain in the stomach and back, along with nausea, vomiting and blood in the urine, indicate pancreatitis. However, increased amylase levels may not occur until after pancreatitis does. The risk of pancreatitis increases with higher doses, more advanced HIV, and alcohol use. Patients experiencing these symptoms should stop taking zalcitabine and seek medical attention immediately. If symptoms clear after stopping zalcitabine, physicians/patients may consider re-starting zalcitabine at a lower dose.

Resistance

HIV mutations that confer resistance to zalcitabine are slow to develop and do not confer a high degree of resistance to zalcitabine. Mutations at codons 184, 75, 74, and 69 of the reverse transcriptase enzyme are associated with resistance to zalcitabine. If a patient develops resistance to zalcitabine, he/she is unlikely to benefit from didanosine.

Recent updates

Mitochondrial toxicity of NRTIs: In vitro assessment and comparison with tenofovir

The effects of NRTIs on cell proliferation, mitochondrial DNA content, and lactate production were determined in human hepatic, skeletal muscle, and renal proximal tubule epithelial cells. Tenofovir was less cytotoxic in hepatic and skeletal muscle cells than ZDV, ddl, ddC, ddI, and abacavir, and was a weaker inhibitor of hematopoietic progenitors than ZDV, ddI, and ddC. The potency of inhibition of mitochondrial DNA synthesis was ddC<did<ZDV>3TC=tenofovir<abacavir. Unlike tenofovir, both ddC and ddI reduced cellular expression of COX II and COX IV. The findings are consistent with the tolerability profiles of NRTI observed in patients with HIV infection.


Fat redistribution in HIV patients on non-protease inhibitor (PI) regimens: Study in six centers in Nigeria

Fat redistribution and other body changes were determined in 87 patients with HIV infection in Nigeria who were PI-naive and receiving other antiretroviral drugs. Drugs used included ddC, ddI, 3TC, ddT, Combivir, and ZDV. Early changes in body shapes appeared after a mean of 32 weeks. Facial fat wasting was the most commonly identified change (46% of patients) at 32 weeks. Increases in abdominal girth, breast, and buffalo hump were first noticed at 36 weeks. Most of the fat wasting was observed in patients receiving ddC (56%) and d4T (66%), and fat accumulation was more frequently observed in patients receiving ZDV (45%) and ddI (55%). Women had less fat wasting and greater increases in buffalo hump and abdominal girth. Body fat redistribution is common in patients with HIV infection on PI-sparing regimens.


The presence of nucleoside analog mutations (NAMs) is highly correlated with reduced susceptibility to all NRTIs

The effects of NAMs and the M184V mutation on susceptibility to all NRTIs were determined in 2,500 samples of HIV-1 with matched phenotypic and genotypic measurements. An increasing number of NAMs was associated with decreased susceptibility to all NRTIs, and the degree of cross-resistance was influenced by the M184V mutation. Based on the effect of the M184V mutation, two NRTI cross-resistance groups were identified: Group 1 (ZDV, d4T, ADV) and Group 2 (ddI, ddC, ABC, 3TC). Among isolates with the same number of NAMs, the M184V mutation generally increased susceptibility to Group 1 NRTIs and decreased susceptibility to Group 2 NRTIs. A 100-fold reduction in ZDV susceptibility was associated with reduced susceptibility to 3TC (6.5-fold), ABC (5.7-fold), d4T (5.3-fold), ADV (4.7-fold), ddI (two-fold), and ddC (1.9-fold). In conclusion, NRTI cross-resistance is highly correlated with the number of NAMs and is modulated by M184V. A reduction in susceptibility to any one NRTI is likely associated with reduced susceptibility to all drugs within this class, albeit at different magnitudes.

At a glance
The first drug approved to treat AIDS, zidovudine was created as a potential treatment for cancer. Zidovudine is metabolized to its active triphosphate metabolite (74% eliminated through the urine). There is cross-resistance between zidovudine and other NRTIs. Its peak effectiveness is in treatment-naive patients as part of a combination regimen. Rash, nausea, headache, bone marrow toxicity (anemia), myopathy, lactic acidosis, and hepatomegaly with steatosis have been reported. Concomitant nephrotoxic, cytotoxic or myelosuppressive drugs should be used with caution.

Potential side effects
Headaches, fever, chills, muscle soreness, fatigue, anemia, nausea, and gingival discoloration. Zidovudine has been associated with bone marrow suppression: anemia and/or neutropenia, particularly in people with advanced HIV. Prolonged use of zidovudine has been associated with symptomatic myopathy (muscle damage). Rare but potentially fatal toxicity with NRTIs merits special warning: pancreatitis, lactic acidosis, and hepatomegaly.

Potential drug interactions
Methadone and ganciclovir (Cytovene and Vitarset) increase zidovudine blood levels. Prescriber may need to adjust doses accordingly. Zidovudine and stavudine (Zent or d4T) should not be used together due to evidence that one limits the other’s bioavailability level in vitro. Also, risk of bone marrow toxicity may increase with use of ganciclovir, amphotericin B (Abelec, Ambisome, or Amphotec), pentamidine (NebuPent or Pentam), dapsone, flucytosine (Ancobon), interferon-alpha ribavirin (Rebetol), and other antineoplastics such as hydroxyurea.

Resistance
Initial zidovudine-resistant mutation is usually at codon 70; followed by mutations at codons 41, 67, 215, and 219. From 5% to 10% of patients on didanosine (Videx or d4T)/zidovudine develop a 151 codon mutation, and a larger number have the T69-SSS insertion; both mutations confer high-level resistance to abacavir (Zagen or ABC), didanosine, lamivudine (Epivir or 3TC), stavudine, zalcitabine (Hivid or dDC), and zidovudine. The M184V mutation that confers high-level lamivudine resistance delays or restores susceptibility to zidovudine, unless there are multiple zidovudine resistance mutations.

Pharmacokinetics
Zidovudine is rapidly absorbed following oral administration, with peak serum concentrations occurring within 0.5 to 1.5 hours. Zidovudine is primarily eliminated by hepatic metabolism. Plasma protein binding of zidovudine is <38%, and the CSF-plasma ratio is 0.6. The elimination half-life of zidovudine is 0.5 hours, and the renal clearance rate is 0.34 L/hr/kg. The AUC of zidovudine is similar when administered as tablets, capsules, or syrup.

Recent updates
Switching stavudine or zidovudine to abacavir for HIV lipodystrophy: A randomized, controlled, open-label, multicenter, 24-week study
A group of 111 patients with HIV infection, HIV RNA <400 copies/ml, and moderate to severe lipodystrophy were randomized to continue current treatment or switch from ZDV or d4T to open-label abacavir in addition to current treatments. All patients were abacavir-naive. At 24 weeks, there were significant increases in limb fat in the abacavir group relative to the continued treatment group, and significant relative increases in subcutaneous thigh and abdominal fat in the abacavir group but not in the continued treatment group. Peripheral fat increases were greater in abacavir-treated patients with higher limb fat mass or lactate <2 mmol/L at baseline. There were no significant changes in patient-assessed lipodystrophy and no correlation between changes in patient-assessed lipodystrophy severity and limb fat mass. Switching to abacavir resulted in relative declines in lactate (p = 0.02) and HIV RNA (p = 0.08). In conclusion, switching from ZDV or d4T to abacavir is associated with improvements in lipodystrophy in HIV-positive adults.


Risk factors and cumulative incidence of anemia among HIV-infected injection drug users
Risk factors for anemia and the cumulative incidence of anemia were determined in a longitudinal cohort study of 662 IDU with HIV infection. At enrollment, 16.1% of men and 30.5% of women (<0.001) were anemic, and 6.7% of men and 14.0% of women had microcytic anemia (p = 0.006). During a median follow-up of 7.5 years, the cumulative incidence of anemia was 82.2%. Factors associated with anemia included older age, female gender (odds ratio [OR] = 1.62), CD4+ count <200 cells mm3 (OR = 1.85), weight loss (OR = 1.55), oral thrush (OR = 1.53), MAC infection (OR = 1.30), and ZDV use (OR = 1.24). Higher body mass index and marijuana use were associated with a lower risk of anemia. Semba RD, Shah N, Vlahov D. Int J STD AIDS 2002;13:119-123.
Brand name
Trizivir™

Class
nucleoside reverse transcriptase inhibitor (NRTI)

FDA approval
November 14, 2000

Form
• 300 mg ABC + 150 mg 3TC + 300 mg ZDV tablet (shown)

Recommended dosage
Adults/adolescents – 1 tablet bid (300 mg ABC + 150 mg 3TC + 300 mg ZDV)
Pediatric – No pediatric labeling.

Note(s)
Not recommended for adults/adolescents who weigh <40 kg.
See ABC, 3TC, and ZDV.

Pregnancy
See ABC, 3TC, and ZDV.

Manufacturer
GlaxoSmithKline

Contact
(888) 825-5249
www.gsk.com

At a glance
Not recommended for patients who weigh less than 40 kilograms, fixed tablet. At 48 weeks, Trizivir was found to be a highly active antiretroviral regimen, generally well tolerated and comparable to indinavir/Crixivan/Combivir (zidovudine/lamivudine) in HIV-infected naïve adults. At 48 weeks, Trizivir/efavirenz (Sustiva) was found to be potent, generally well tolerated (with no adverse events other than those previously described with drugs in this regimen), and associated with good adherence (industry-sponsored study: 60% of patients were either African American or Latino, treatment naïve with advanced stage of HIV disease). ACTG 5095 comparing Trizivir versus Trizivir/efavirenz versus Combivir/efavirenz is underway.

Potential side effects
See zidovudine, lamivudine, and abacavir.

Drug interactions
See zidovudine, lamivudine, and abacavir.

Resistance
See zidovudine, lamivudine, and abacavir.

Pharmacokinetics
See zidovudine, lamivudine, and abacavir.

Recent updates
Switch to Trizivir versus continued HAART provides equivalent HIV-1 RNA suppression at 48 weeks (TRIZAL - AZL 30002)
A group of 209 patients with HIV infection were randomized to continue receiving triple HAART or switch to Trizivir. The most common pre-study regimen was two NRTI + PI. All patients had HIV RNA <400 copies/ml for the previous six months and HIV RNA <50 copies/ml at study enrollment. At week 48, the proportion of patients with treatment failure (two consecutive plasma HIV RNA values >400 copies/ml) was 22% in both groups. Virologic failure occurred in the first 24 weeks in five Trizivir patients and one continued HAART patient. Premature discontinuation occurred in 18 patients receiving Trizivir and 22 patients receiving continued HAART. Significantly greater reductions in total cholesterol and triglyceride levels were observed in the Trizivir group, and patients in the Trizivir group reported their regimen was easier to take. In conclusion, switching to Trizivir offers a potent and simplified regimen with equivalent efficacy as compared with continued HAART.

Abacavir/Combivir (ABC/COM) is comparable to indinavir/Combivir (IDV/COM) in HIV-1-infected antiretroviral therapy naïve adults: Preliminary results of a 48-week open-label study (CNA 3014)
In an open-label trial, 342 patients with HIV infection who were treatment-naïve were randomized to receive Trizivir bid or indinavir/Combivir (800 mg three times daily/four tablets twice daily). The median baseline HIV RNA and CD4+ count was about 4.80 log copies/ml and 315 cells/mm3 in both groups, respectively. At 48 weeks, the proportion of patients with HIV RNA <400 copies/ml was 66% in the Trizivir group and 50% in the indinavir group (p = 0.002). In patients receiving Trizivir, HIV RNA <50 copies/ml at 48 weeks was achieved by 90% of those with baseline HIV RNA 5000 to 100,000 copies/ml and 59% of those with baseline HIV RNA >100,000 copies/ml. In patients receiving indinavir, HIV RNA <50 copies/ml at 48 weeks was achieved by 73% of those with baseline HIV RNA >100,000 copies/ml. CD4+ count increases were 148 and 152 cells/mm3 in the Trizivir and indinavir groups, respectively. The discontinuation rate was 21% and 38% in the Trizivir and indinavir groups, respectively, and adherence >95% at weeks 44 to 48 was reported by 72% of those in the Trizivir group and 45% of those in the indinavir group.
At a glance
Tenofovir is the first nucleotide analog approved for HIV-1 treatment. Chemically related to adefovir (GS 5940), no significant renal toxicity reported. At 48 weeks, adding tenofovir to existing antiretroviral therapy in highly treatment-experienced patients shows significant and durable HIV RNA reductions. There is an infrequent development of reverse transcriptase mutations associated with tenofovir.

Potential side effects
Grade 3 or 4 (serious) increased creatine (a sign of kidney or muscle damage) and AST/ALT (liver function tests, a sign of liver damage) shown in lab reports. In one study, serious side effects ranged from 6% to 16%. However, this range was not statistically different from the placebo arms. These side effects include elevation of creatine phosphokinese (CPK), nausea, headache, diarrea, vomiting, asthma, anemia, abdominal pain, and anorexia. Rare but potentially fatal toxicity with NRTIs merits special warning: pancreatitis, lactic acidosis, and hepatic steatosis.

Potential drug interactions
None known.

Resistance
Tenofovir does not appear to select new resistance mutations in the vast majority of people who add the drug to a failing regimen. Genotypic analysis from the 907 study found that only four of the patients with detectable viral load had developed a K65R mutation, which has been previously defined as associated with nucleotide analog use. The presence of the D67N, K70R, T215F, or K219Q/EN mutations associated with NRTI resistance at baseline did not affect response to tenofovir, but the M41L and L210W mutations did reduce the response to tenofovir in the 902 and 907 studies. These findings suggest that it may be possible to use tenofovir as salvage therapy to limit viral rebound without necessarily compromising its future combination with new drugs. NRTI resistance is partly attributable to the removal of the nucleoside analog from the reverse transcriptase enzyme, but tenofovir appears less easily removable, and this may explain why the drug is active against virus that is resistant to other nucleoside analogs. Laboratory studies suggest that virus that is resistant to nucleoside analogs (with the Q151M multidrug resistant mutation) will still be sensitive to tenofovir, and if the drug is used post-chronic acquiring resistance and has often used in combination with ritonavir containing therapy. Despite this, the presence of the M184V mutation in the context of other drug resistance mutations seems to improve sensitivity to tenofovir, leading some researchers to suggest that it may be appropriate to maintain lamivudine and abacavir treatment in order to preserve this mutation.

Pharmacokinetics
The oral bioavailability of tenofovir is 25%, and the pharmacokinetics are dose-proportional. Cmax is achieved in 1.0 hours. Binding of tenofovir to human serum or plasma proteins is <7%. Tenofovir is not a substrate of CYP450 enzymes, and the route of elimination is primarily renal.

Recent updates
Tenofovir DF: A 48-week final analysis from a phase III randomized, double blind placebo controlled study in antiretroviral-experienced patients
In a multicenter, double-blind study, 550 treatment-experienced patients with HIV infection received TFV (300 mg once daily) or placebo for 48 weeks in addition to stable background antiretroviral therapy. After week 24, all patients received open-label TFV through 48 weeks. The mean baseline HIV RNA and CD4+ count was 4,457 copies/ml and 427 cells/mm3, respectively. Baseline resistance mutations were 94% NRTI, 58% PI and 48% NNRTI. At 48 weeks, the proportion of patients with HIV RNA <400 copies/ml and ≤50 copies/ml was 41% and 18%, respectively. The mean increase in CD4+ counts at 48 weeks was 13 cells/mm3. The proportion of patients with grade 3/4 adverse events and grade 3/4 laboratory abnormalities was 20% and 35%, respectively. At 48 weeks, 3% of patients developed the tenofovir-associated K65R resistance mutation. No evidence of drug-related renal toxicity was observed. Squires K, Piorone G, Berger D, et al. 9th Conference on Retroviruses and Opportunistic Infections. February 2002, Seattle. Abs. 413-W.

Effect of baseline nucleoside-associated resistance on response to tenofovir DF (TDF) therapy: Integrated analyses of studies 902 and 907
Baseline plasma samples from 470 treatment-experienced patients with HIV infection who were randomized to receive TFV (300 mg/day) or placebo in addition to stable background therapy for 48 weeks were analyzed for the effect of specific thymidine analog mutations (TAMs) and TFV susceptibility on the response to TFV. Significant reductions in HIV RNA at 48 weeks were observed in patients with 0 to 4 or more TAMs at baseline. Responses to TFV were diminished in patients with ≥3 TAMs inclusive of either the M41L or L210W mutation or the L210W mutation in any context. Mutations at positions 67, 70, or 219 did not affect the response to TFV. Baseline phenotypes from 138 patients showed mean reduced susceptibility from wild-type of 1.8-fold for TFV and 10-fold for ZDV. Patients with > four-fold reduction in TFV susceptibility at baseline (9%) showed diminished responses to TFV therapy, and recursive partitioning analysis confirmed a break-point of four-fold for response to TFV. Genotypic analysis of HIV with > four-fold reduced susceptibility to TFV revealed a K65R mutation, a T215 double insertion, or multiple TAMs (M41L and/or L210W). Adding TFV to an existing regimen shows significant and durable reductions in HIV RNA in patients with M184V and/or multiple TAMs. Reduced responses to TFV are associated with specific TAM patterns or > four-fold reduced susceptibility to TFV at baseline.

Safety profile of tenofovir disoproxil fumarate (TDF) in patients with advanced HIV disease
A group of 291 patients with advanced HIV infection received open-label TFV in addition to background antiretroviral therapy. Clinical and laboratory adverse events (AEs) were assessed monthly. At baseline, mean HIV RNA and CD4+ count was 4.87 log copies/ml and 36 cells/mm3, respectively. With a mean and maximum duration of TFV of 25 weeks and 42 weeks, respectively, 8% of patients discontinued treatment due to AEs, 3% died, and 15% experienced a serious AE. Except for pneumonia (3%), no serious AE was observed in >1% of patients. The most common grade 3/4 AEs were diarrhea (4%) and pneumonia (4%). The grade 3/4 laboratory abnormality was elevated triglycerides. In patients with and without prior adefovir dipivoxil use, the mean change in serum creatinine from baseline at week 24 was +0.06 and +0.09 mg/dL, respectively. In conclusion, TFV can be safely administered as part of a PI-based HAART regimen to heavily treated patients with advanced HIV infection. Bedor S, Ruane P, Cimoch P, et al. 43rd ICAAC. December 2001, Chicago. Abs. 1930.
At a glance
There is an antagonistic effect between stavudine and zidovudine. Extended release formulation has been found to be safe and effective. The major clinical toxicity of stavudine is peripheral neuropathy (up to 24%). All nucleoside analogs induce mitochondrial toxicity. Lactic acidosis and severe hepatomegaly with steatosis have been reported with stavudine use (possible risk factors include female gender, obesity, and prolonged nucleoside exposure). Lipatrophy is of major concern in patients with thymidine analog (stavudine and zidovudine) containing regimens. Withdrawal of thymidine analogs in lipoprotein patients on a protease inhibitor-sparing regimen results in a significant improvement in peripheral fat stores, and is associated with loss of virological control. Stavudine crosses the blood-brain barrier to a useful degree, which may treat or prevent neurological damage.

Potential side effects
Headache, chill/fever, malaise, insomnia, anxiety, depression, rash, nausea, vomiting, diarrhea, abdominal pain, and peripheral neuropathy. Symptoms may persist after stopping the drug. If symptoms go away after stopping stavudine, consider starting stavudine again at a smaller dose. Caregivers of young children should be instructed regarding noticing and reporting peripheral neuropathy. Adverse reactions and serious laboratory abnormalities in pediatric patients were similar in type and frequency to those seen in adults. Rare but potentially fatal toxicity with NRTIs merits special warning: pancreatitis, lactic acidosis, and hepatic steatosis.

Potential drug interactions
Drugs such as amphotericin B (Fungizone), foscarnet (Foscavir), and dapsone may increase the risk of developing peripheral neuropathy. Ganciclovir (Cytovene or Viramist) and intravenous pentamidine (Fenestra) may increase the risk of pancreatitis. Stavudine is to be used with caution by patients with pre-existing bone marrow suppression, renal insufficiency, or peripheral neuropathy. When combined, didanosine (Videx or ddI) and hydroxyurea (Hydrea) may increase risk of pancreatitis. Zidovudine and stavudine should not be used together due to evidence that one limits the other's bioavailability level in vitro.

Resistance
There is a growing body of evidence that the extent of resistance to stavudine has been underestimated. Virco has reported that at least 26 mutations, including zidovudine-associated mutations, are associated with stavudine resistance. Early resistance tests looked at only nine mutation sites and so underestimated the extent of stavudine resistance. Virco has also reviewed estimates of significant resistance. The cut-off for stavudine resistance using the Antivirogram assay has been adjusted downwards, so that 3.0-fold resistance to stavudine is now considered significant. Mutations that cause specific resistance to stavudine do occur, including 62V, 69V, 69D, 69KX, 75I, 75T, 116Y, and 151M. Treatment with stavudine may also cause zidovudine-associated resistance mutations. The resistance mutation 151 causes resistance to all the NRTIs, including stavudine, and may emerge during treatment with stavudine.

Pharmacokinetics
C_max and AUC increase in proportion to the dose after both single and multiple doses ranging. Stavudine is rapidly absorbed, with peak plasma levels occurring within one hour after dosing. Binding of stavudine to plasma proteins is negligible. Renal elimination accounts for about 40% of the overall clearance.

Recent updates
Pharmacokinetics (PK) of stavudine (d4T) extended release formulation compared with stavudine immediate release (IR) formulation as part of potent antiretroviral combination therapy
The pharmacokinetics of a once-daily formulation of extended-release d4T (d4T-XR) were compared with those of the currently available immediate release formulation (d4T-IR) in 16 treatment-naive patients with HIV infection. d4T-XR was administered at a dose of 100 mg/day, and d4T-IR was administered at a dose of 40 mg bid. Both drugs were administered in combination with NRTI and NNRTI. For both d4T formulations, C_max, T_max, and AUC were similar on days one and 14. The geometric mean C_max was about 50% lower for d4T-XR than for d4T-IR, but the geometric mean total daily exposure of d4T-XR and d4T-IR were similar. Geometric mean C_min was 5.5 times higher for d4T-XR than for d4T-IR. There was a lack of accumulation of d4T-XR and d4T-IR following multiple dosing. In conclusion, d4T-XR provides drug exposure that is reasonably similar to d4T-IR. The pharmacokinetic profile of d4T-XR supports once-daily dosing. Kaul S, Damle B, Gale J, et al. 9th Conference on Retroviruses and Opportunistic Infections. February 2002, Seattle. Abs. 430-W.

Stavudine XR versus stavudine IR as part of potent antiretroviral combination therapy: 24-week safety and antiviral efficacy
In a prospective study, 797 treatment-naive patients with HIV infection were randomized to receive d4T in extended-release (d4T-XR) or immediate-release (d4T-IR) formulations in combination with 3TC and efavirenz. The median baseline HIV RNA and CD4+ count were 4.8 log copies/ml and 277 cells/mm^3, respectively. At 24 weeks, the mean decrease in HIV RNA (0.79 log copies/ml) was identical in both groups, and the mean increase in CD4+ counts was 142 cells/mm^3 in the d4T-XR group and 136 cells/mm^3 in the d4T-IR group. The safety and tolerability of d4T-XR were similar to those of d4T-IR. At 24 weeks, 3% of patients in each group discontinued treatment due to adverse events. Grade 3/4 clinical adverse events were similar in both groups. In conclusion, d4T-XR is well tolerated and provides a safety and antiretroviral profile similar to that of d4T-IR over 24 weeks of dosing when used as part of potent combination therapy in treatment-naive patients. Pollard R, Iwe P, Farthing C, et al. 9th Conference on Retroviruses and Opportunistic Infections. February 2002, Seattle. Abs. 411-W.
Vanity Fair readers have every month since 1993 enjoyed *The Proust Questionnaire*, a series of questions posed to celebrities and other famous subjects. The Vanity Fair questionnaire—modeled after a questionnaire Marcel Proust was asked to fill out in the late 1800s—reveals much about the respondents’ lives, thoughts, values, and experiences. In May 2002, IAPAC Monthly introduced “In the Life,” through which IAPAC will feature members who have been asked to bare their souls through their answers to ten questions.

This month, IAPAC Monthly is proud to feature Bob Colebunders, Professor of Tropical Diseases at the Institute of Tropical Medicine in Antwerp, Belgium.

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

“Imagine,” the song by John Lennon

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

I like running, cycling, and enjoying nature (mainly the mountains). I love my wife and two children and I would like to spend more time with them. I have no hidden talent.

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

I prefer living in a democratic country, with little social injustice, nice weather, beautiful mountains, nice beaches, a large budget for healthcare, clinical research, and support for resource-poor countries. Moreover, I would like to live in such a country with my family and friends. I am afraid that such an ideal country does not exist. For the moment I am not unhappy in Belgium.

Who are your mentors or real life heroes?

There are certainly real life heroes but I do not know them personally. Most people have good and bad qualities and sometimes too many people want to be heroes. As my mentors I would like to mention the late Henri Taelman, a clinician at the Institute of Tropical Medicine, and Kapita Bila, a clinician from Kinshasa, Democratic Republic of Congo, [both of whom] were among the first to recognize AIDS among African patients; and Peter Piot who started AIDS research at the Institute of Tropical Medicine and who gave me the opportunity to join his team.

With what historical figure do you most identify?

I do not identify myself with a historical figure. Moreover I prefer to look into the future and not into the past.

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

I have very little time to read [literature] other than scientific literature; I prefer modern arts and modern music.

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

For most people, certainly in the developed world, it is probably better to live now than in any other time period in human history. I would rather come back in the future if that were possible.

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

An engineer.

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

[Our] greatest achievements [relate to] scientific progress. In the developed world, living conditions have improved for a large number of people because of improved healthcare - people live longer and healthier. We are able to travel all over the world very quickly, we have new communicating tools, and computers do part of our work. However, the gap between the rich and the poor is increasing, war and social injustice continue, [and] there is still a lot of racism and lack of solidarity.

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

Scientifically we will make progress at [an even] more rapid speed than before, but the trends we have seen in the past 10 years will continue. Despite certain nice speeches of our world leaders, the gap between the rich and the poor will continue to increase. Persons in Africa will have a very difficult time. AIDS may become a controllable disease in the developed world, but suffering because of AIDS will continue to increase in resource-poor countries.

Bob Colebunders

*IAPAC Monthly* July 2002
In June 2002, the International Association of Physicians in AIDS Care (IAPAC) welcomed 28 physician and 14 allied health professional new and renewing dues-paying members from five countries. IAPAC thanks the following individuals for their support of the association’s mission to improve the quality of care provided to all men, women, and children living with HIV/AIDS.

Irene K. Adams, Brazil
Kimberly Betty, USA
Maurizio Bonacini, USA
Kathleen A. Clanon, USA
Robert W. Clausen, USA
Randall Conn, USA
Frehiwot Derso, USA
Dan Eide, USA

Wendy Forman, USA
James H. Hinrichs, USA
Robert Hoffman, USA
Fran Kalafatis, USA
Dale Kummerle, USA
Lori Mahler, USA
Irene Wanjiku Maina, USA
Anil T. Mangla, USA
Lawrence M. McGlynn, USA
Jason Morhart, USA
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Robert A. Myers, USA
Estelita M. Quimosing, USA
William C. Sanchez, USA
David Stein, USA
Joseph Thurn, USA
Frank Tomaka, USA
Abdulla Mehmood Ustadi, UAE
Jonathan Weiss, USA
Kevin Young, USA
James A. Zachary, USA

Lee Francis, USA
Jerome Franz, USA
Marc N. Gourévitch, USA
Jane N. Munyi, Kenya
Robert A. Myers, USA
Estelita M. Quimosing, USA
William C. Sanchez, USA
David Stein, USA
Joseph Thurn, USA
Frank Tomaka, USA
Abdulla Mehmood Ustadi, UAE
Jonathan Weiss, USA
Kevin Young, USA
James A. Zachary, USA

To learn more about IAPAC individual physician and/or allied health professional membership, please contact Joey Atwell, Director of Membership, at (312) 795-4941 or jatwell@iapac.org.

Do you wish to strengthen the profession, enhance your colleagues’ work, and win a prize? Your recruitment effort will not go unrecognized. Each time you recruit a new member, your name will be entered into a drawing to win one of the following prizes:

- One roundtrip, upgradable, tourist class ticket anywhere United Airlines flies in the United States.
- One roundtrip, upgradable, tourist class ticket anywhere United Airlines flies in Europe.

From March 1, 2002, to December 15, 2002, the more new members you recruit, the greater your chances of winning! Plus, you will receive recognition in the IAPAC Monthly.

Whether you sponsor one or 100 new members, you will receive a gift as recognition of your contribution to the success of this IAPAC membership campaign. There are four sponsorship levels; at the end of the campaign, you will receive a prize for the recruitment level you have met.

- **Level 1** - Recruit one to four new members between March 1, 2002, and December 15, 2002, and receive an IAPAC lapel pin.
- **Level 2** - Recruit five or more new members between March 1, 2002, and December 15, 2002, and receive an IAPAC lapel pin and a custom-designed plaque recognizing your commitment to IAPAC.
- **Level 3** - Recruit 20 or more new members between March 1, 2002, and December 15, 2002, and receive Level 1 and 2 gifts and a 12-month complimentary extension of your IAPAC membership.
- **Level 4** - Recruit 75 or more new members between March 1, 2002, and December 15, 2002, you may show off your accomplishment with a 10k yellow gold IAPAC lapel pin (and receive Level 2 and 3 gifts).

There is Strength in Numbers—encourage others to become IAPAC members. It is easy. To learn how easy, contact IAPAC’s Membership Department at (312) 795-4941 or e-mail membership@iapac.org.
[Strength in Numbers]

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[ ] Physician — US$140
• 12 issues IAPAC Monthly
• 4 issues J IAPAC
• Educational supplements/clinical management materials
• Preferred invitations to IAPAC-sponsored conferences
• Access to “Members Only” section of the IAPAC Web site

[ ] Non-Physician — US$120
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or visit www.iapac.org
Two years ago this month...

at the XIII International AIDS Conference in Durban, South Africa

I exist as a living embodiment of the inequity of drug availability and access in Africa.
South African Justice Edwin Cameron during an impassioned address delivered at the conference’s July 9, 2000, opening plenary. Cameron, a member of his nation’s highest court and one of the most prominent South Africans to speak openly about living with HIV/AIDS, lambasted international agencies, national governments, and the pharmaceutical industry for not doing enough to expand access to treatment.

With opportunity comes responsibility and challenge. There are no more excuses.
Gro Harlem Brundtland, Director-General of the World Health Organization (WHO), during a July 11, 2000, satellite meeting at which she outlined WHO activities to combat the HIV/AIDS pandemic. Brundtland said that millions of people living with and at risk for HIV infection “will not forgive us if the world does not take advantage of the opportunities for action that exist today.”

Just a couple of years ago this would have been unimaginable.
Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID), an agency of the US National Institutes of Health (NIH), observing that an important aspect of the XIII International AIDS Conference was discussion of considering highly active antiretroviral therapy (HAART) in developing countries.

It is important for the community at large to recognize that this movement on drug pricing has taken place as a direct result of the pressure that has been applied to the pharmaceutical industry.
José M. Zuniga, President of the International Association of Physicians in AIDS Care (IAPAC), during a July 10, 2000, panel discussion at which physicians from developed and developing countries shared their experiences with antiretroviral therapy. IAPAC was among many civil society institutions at the conference that advocated machinations of change to allow for greater access to less expensive antiretroviral drugs in resource-limited settings.