Protease Inhibitor Therapy: Boosted and Double-Boosted Options to the Fore

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In April 1999, Dr. Schlomo Staszewski had a simple message for clinicians attending his first PRN lecture: that protease inhibitors were a less-than-ideal therapeutic option and that focus should be placed on prescribing protease inhibitor-sparing regimens, whenever possible. "We were seeing problems with dosing, with side effects, with dietary restrictions, with resistance and cross resistance," Dr. Staszewski said upon returning to PRN in November 2003. "For these and other reasons, I tried to explain that we shouldn't be using protease inhibitors anymore. I don't want to be viewed as an opportunistic guy, that I change my opinions every time I get up to talk. But times have changed and our patients have changed. There's a new perception of protease inhibitors and we're seeing that these drugs can now be used more effectively than when they were first approved."

Protease inhibitors remain an extremely valuable therapeutic option. There is certainly no shortage of data indicating that protease inhibitors have played an enormous role in decreasing mortality and morbidity while at the same time significantly enhancing the overall quality of life of most people living with the virus. However, protease inhibitors also have several disadvantages, all of which have been well documented. First, protease inhibitor therapy often comes with a high pill burden, complex dosing schedules, and careful dietary considerations. Second, they are associated with a growing number of short- and long-term side effects, including diabetes and other metabolic complications. In turn, a snowball effect can ensue: Each of these potential drawbacks has been associated with nonadherence, which can ultimately cause resistance and cross-resistance, virologic failure, lack of therapeutic options, and disease progression.

However, a great deal of data generated over the past several years have brought about a sea change in the way these drugs are used. Pharmacokinetic "boosting"—the use of ritonavir (Norvir) to boost concentrations of other protease inhibitors—has, in effect, rendered many of these drugs easier to take and more effective. Research is also emerging regarding the use of two protease inhibitors—both boosted using low-dose ritonavir—as a therapeutic option, which appears to hold promise, particularly for patients who have tried and failed protease inhibitor therapy in the past.

The Value of Boosting

The need to improve both the convenience and effectiveness of protease inhibitors led to the use of ritonavir as a pharmacologic enhancer. Ritonavir is an ideal pharmacologic enhancer because it inhibits two key stages of metabolism. First, ritonavir inhibits what is known as first-pass metabolism, which occurs during absorption. Enterocytes that line the intestine contain both CYP3A4, one of the key isoenzymes associated with drug metabolism, and P-glycoprotein, an efflux transporter that can effectively pump drugs out of the gut wall and back into the intestinal lumen. Ritonavir appears to inhibit both of these proteins and, consequently, may increase a coadministered drug's C_{max}. Second, ritonavir inhibits CYP3A4 in the liver, thereby maintaining a drug's half-life. It is also possible that ritonavir inhibits P-glycoprotein found in CD4+ cells. As a result, less drug is transported back out of the cell, thereby increasing the drug's intracellular half-life.

"Even though ritonavir was one of the first protease inhibitors to demonstrate a survival advantage, it is no longer used at its intended therapeutic dose of 600 mg twice a day," Dr. Staszewski said. "The side effects of ritonavir at this dose are really quite profound and the drug quickly fell out of favor among many patients and health-care providers. But ritonavir has been remarkable as a boosting agent. It can improve the pharmacokinetic profiles of the other protease inhibitors, which means that we can now treat our patients with fewer pills and longer dosing intervals, such as twice a day or once-daily dosing. This is much more convenient. What is also very important is that we now have greater potency against protease inhibitor-resistant virus, which is likely the result of increased exposure to the drugs."

It is important to note that the benefit of pharmacologic enhancement using ritonavir depends on the coadministered protease inhibitor being used. With saquinavir (Invirase; Fortovase) and lopinavir (Kaletra), for example, ritonavir's greatest contribution is its ability to boost their C_{max} concentrations (see Figure 1). Alternatively, ritonavir's favorable

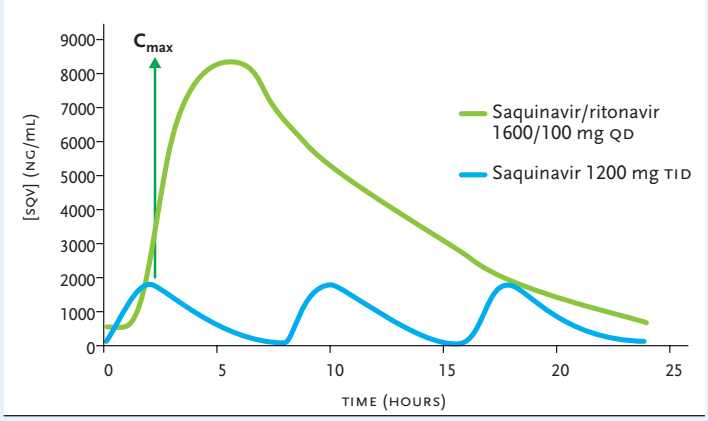

FIGURE 1. C_{max} Boosting with Ritonavir: For PIs with Poor Intrinsic Bioavailablility

Ritonavir inhibits first-pass metabolism, which occurs during absorption. Enterocytes that line the intestine contain both CYP3A4, one of the key isoenzymes associated with drug metabolism, and P-glycoprotein, an efflux transporter that can effectively pump drugs out of the gut wall and back into the intestinal lumen. Ritonavir can inhibit both of these proteins and, consequently, may increase a coadministered drug's C_{max}. This is an advantage when ritonavir is combined with protease inhibitors suffering from poor intrinsic bioavailability, such as saquinavir (shown here) or lopinavir.

Source: Schlomo Staszewski, MD

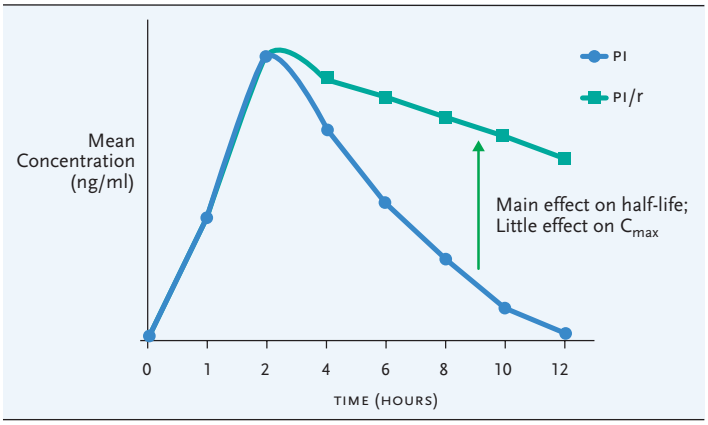

FIGURE 2. **Half-Life Boosting with Ritonavir: For PIs with Good Bioavailablility but Short Half-Lives**

Ritonavir inhibits CYP3A4 in the liver, thereby maintaining a drug's half-life. This is a significant advantage when ritonavir is combined with protease inhibitors with good oral bioavailability but short half-lives, such as indinavir, amprenavir, and to a lesser degree nelfinavir.

Source: Schlomo Staszewski, MD

pharmacokinetic blend with indinavir (Crixivan), amprenavir (Agenerase), and to a lesser extent nelfinavir (Viracept), is its prolongation of their half-lives (see Figure 2).

Ritonavir Boosting: The Experience in Clinical Trials

SOLID DATA FROM CLINICAL TRIALS EVALUATING RITONAVIR-BOOSTED protease inhibitor regimens have emerged in recent years. Lopinavir/ritonavir (lopinavir/r; Kaletra), for example, has been shown to be an effective option for patients failing an initial protease-inhibitor based regimen. In one study (M97-765), the safety and antiviral activity of lopinavir/r were evaluated in 70 NNRTI-naive patients with HIV-RNA levels between 1,000 and 100,000 copies/mL while on a first protease inhibitor-based regimen (Benson, 2002). Patients were randomized to substitute only the protease inhibitor with lopinavir/r, 400/100 mg or 400/200 mg twice daily. On day 15, nevirapine was added, and nucleoside reverse-transcriptase inhibitors were changed. Despite a greater than fourfold reduction in phenotypic susceptibility to the previously used protease inhibitor in 63% of patients, mean HIV-RNA levels declined by 1.14 log copies/mL after two weeks of lopinavir/r. At week 48, 76% of subjects receiving treatment had HIV-RNA levels below 50 copies/mL—one of the most substantial and durable responses ever seen in patients switching from one protease inhibitor to another because of virologic failure.

There are also data from the MaxC_{min}2 study, a head-to-head comparison of two boosted protease inhibitors: lopinavir/ritonavir and saquinavir/ritonavir. Of the 339 patients enrolled in the study, approximately 32% had failed an initial protease-inhibitor based regimen prior to entering the trial. The risk of virologic failure was significantly higher in the saquinavir/ritonavir group, compared to the lopinavir/ritonavir group, in the intent-to-treat analysis (ITT/e, which included all randomized patients who took at least one dose of the assigned treatment). And after 48 weeks of treatment, 65% of patients in the lopinavir/ritonavir group—compared to 57% of patients in the saquinavir/ritonavir group—had HIV-RNA levels below 50 copies/mL in the ITT/e analysis. However, this difference was not statistically significant.

Ritonavir-boosted atazanavir (Reyataz) has also been evaluated as a contender for patients with prior protease inhibitor experience. In one 48-week study (BMSAI424-045) reported at the 11th Conference on Retroviruses and Opportunistic Infections (CROI), held this past February in San Francisco, 358 patients with a history of multiple treatment failures were randomized to receive either atazanavir (300 mg QD) plus ritonavir (100 mg QD), atazanavir (400 mg QD) plus saquinavir (Invirase) (1200 mg QD), or standard doses of lopinavir/ritonavir (Kaletra) (DeJesus, 2004). All patients also received tenofovir plus one nucleoside reverse transcriptase inhibitor.

At baseline, the median viral load was 4.4 log copies/mL and the CD4+ count was approximately 300 cells/mm^3. After 48 weeks of treatment, the intent-to-treat analysis indicated that 36% of patients in the atazanavir/ritonavir group and 42% of patients in the lopinavir/ritonavir group had HIV-RNA levels below 50 copies/mL, with no statistically significant differences between the two. Similarly, actual viral load reductions were similar in both groups (–1.93 log copies/mL in the atazanavir/ritonavir group and –1.87 in the lopinavir/ritonavir group). Patients in the atazanavir/saquinavir arm had a less impressive showing: only 24% had HIV-RNA levels below 50 copies/mL, and the median viral load reduction was 1.55 below baseline values after 48 weeks of therapy.

A number of ritonavir-boosted protease inhibitor dosing schedules have been defined (see Table 1).

TABLE 1. **Common Dosing Regimens for Ritonavir-Boosted Protease Inhibitors**

Protease Inhibitor	Dose
Lopinavir/ritonavir (Kaletra)	400 mg/100 mg (3 pills) BID*
Saquinavir/ritonavir	1000 mg/100 mg (6 pills) BID*
	1600 mg/200 mg (10 pills) QD
Amprenavir/ritonavir	600 mg/100 mg (5 pills) BID*
	1200 mg/200 mg (10 pills) QD*
Fosamprenavir/ritonavir	700 mg/100 mg (2 pills) BID*
	1400 mg/200 mg (4 pills) QD*
Indinavir/ritonavir	800 mg/100 mg (3 pills) BID
	400 mg/100 mg (2 pills) BID
Atazanavir/ritonavir	300 mg/100 mg (3 pills) QD

* Dosing approved by the U.S. Food and Drug Administration

The QUAD Study

THE QUAD STUDY, CHAIRED BY DR. STASZEWSKI, WAS A RANDOMIZED, open-label evaluation of ritonavir-boosted saquinavir (1000 mg saquinavir BID, 100 mg ritonavir BID) combined with either Combivir or Trizivir in antiretroviral-naive patients with high viral loads and low CD4+ cell counts (Staszewski, 2003). "We wanted to test a standard ritonavir-boosted triple-drug regimen against an even more potent ritonavir-boosted quadruple-drug regimen in these patients with advanced HIV disease," Dr. Staszewski explained. "We don't have a lot of experience treating treatment-naive patients with progressed HIV disease. We wanted to know if it's best to treat these patients with a four-drug regimen or a three-drug regimen."

Fifty-nine patients were randomized, with 30 receiving the Combivir regimen and 29 receiving the Trizivir regimen. Viral loads upon entering

the study were approximately 300,000 copies/mL in both groups; the CD4+ count was generally between 20 and 35 cells/mm^3.

After 48 weeks of treatment, 18 patients in the Combivir group and 17 patients in the Trizivir group remained on stable therapy. Four and five patients in each group respectively switched to another regimen; six and four patients respectively discontinued therapy altogether. In the as-treated analysis—which included all patients remaining on stable therapy after 48 weeks—100% of patients in the Trizivir group and 95% of patients in the Combivir group had HIV-RNA levels below 400 copies/mL. In the intent-to-treat analysis—which included all patients, including those who either switched or discontinued therapy—60% in both groups had HIV-RNA levels below 400 copies/mL after 48 weeks.

"This study demonstrated that boosted saquinavir, in combination with either Combivir or Trizivir, is highly active and well tolerated in patients with high viremia and low CD4+ cell counts," Dr. Staszewski commented. "Of interest, no virologic failure associated with resistance occurred with the regimens applied in this study. This is in concordance with other studies that have evaluated boosted protease inhibitors for initial treatment and this is something we really need to think about and to look for in future studies. For example, it will be very interesting to look at boosted and unboosted atazanavir in initial treatment. Because atazanavir is now used frequently in initial treatment, we have to compare both regimens with regard to the emergence of resistance."

Protease Inhibitor-Only Regimens

WHILE NOT ON THE RADAR SCREEN OF YOUR TYPICAL HIV-TREATING CLINician, there has been much interest in regimens consisting only of protease inhibitors within the research community. Studies of boosted protease inhibitors—without concomitant nucleoside reverse transcriptase inhibitors (NRTIs)—have helped to define the potency of such pairings and have also contributed evidence that protease inhibitors may not be solely to blame for the metabolic and morphologic complications that have come to be associated with antiretroviral therapy.

Abbott Study M96-462

M96-462, AN ABBOTT-SPONSORED STUDY, RANDOMIZED 141 HIV-POSITIVE patients with CD4+ counts between 100 and 500 cells/mm^3—all of whom were naive to protease inhibitor therapy—to receive one of four NRTI-sparing regimens consisting of saquinavir and ritonavir (either 400/400 mg BID, 600/400 mg BID, 400/400 mg TID, or 600/600 mg BID). Patients were permitted to intensify their regimen under the following conditions: a viral load that was still above 200 copies/mL after 12 weeks of dual-protease inhibitor therapy; a viral load that was once undetectable and rebounds to a detectable level; a viral load that decreased at least one log from baseline and subsequently rebounded. After 48 weeks of dual-protease inhibitor therapy, all patients were permitted to intensify their regimen with NRTIs, at the discretion of the study coordinator.

Five-year follow-up data was reported at the 9th CROI, held in 2002 in Seattle (Cameron, 2002). Of the original cohort, 120/139 (86%) evaluable patients experienced viral load reductions below 200 copies/mL at some point during the study. Through year five, 54/66 (82%) evaluable patients remaining in the study have viral loads below 200 copies/mL, with a median CD4+ count increase of 381 cells/mm^3 from baseline.

While many elected for NRTI intensification after 48 weeks, 32/66 (48%) patients remained on saquinavir/ritonavir—without NRTIs—through year five. The percentage of NRTI-sparing and NRTI-intensified subjects with viral loads below 200 copies/mL after five years was 88% and 84% respectively. Between years four and five, 1/66 (2%) patients on study required NRTI-intensification and 17/83 (20%) patients discontinued, three because of adverse events and 14 for other reasons. "These data basically showed us that dual protease inhibitor therapy, either with or without added NRTIs, has durable activity for up to five years."

Also of interest are follow-up data from study M96-462 looking at morphologic changes in patients receiving dual-protease inhibitor therapy. These data were reported at the 9th CROI by Dr. Calvin Cohen (Cohen, 2002). A standardized questionnaire and physical examinations for morphologic abnormalities were administered from year three to year five. Again, 66 patients remained in the study after five years of treatment and 32 had intensified therapy with NRTIs at some time prior to that point. The prevalence of the most common morphologic abnormalities after five years of treatment for NRTI-intensified versus NRTI-sparing regimens was: buttock wasting (9/32 [28%] vs. 2/34 [6%]) and thinning of the cheeks (11/32 [34%] vs. 2/34 [6%]) respectively.

Reports of morphologic abnormalities also increased over time. For example, at year three, 25% of NRTI-intensifying patients reported thinning of the cheeks, compared to 34% of NRTI-intensifying patients at year five. As for wasting in the upper and/or lower extremities, 6% of NRTI-intensifying patients reported this at year three, which ballooned to 22% at year five. As for patients who remained off NRTIs, 3% reported thinning of the cheeks at year three, compared to 5% at year five. There were no reports of wasting in the lower extremities, with 9% of NRTI-sparing patients reporting thinning of the legs at year five. Self-reported, exam-confirmed presence of at least three morphologic abnormalities at year five for NRTI-intensified versus NRTI-sparing regimens was 10/32 (31%) and 2/34 (6%), respectively.

Prometheus Study

THE PROMETHEUS STUDY WAS A MULTICENTER, OPEN-LABEL, RANDOMIZED controlled trial that enrolled 208 HIV-positive patients who had not been given a protease inhibitor or stavudine (Zerit) therapy prior to enrollment (van der Valk, 2001). All patients received both ritonavir (400 mg BID) plus saquinavir (400 mg BID). Half of the patients were randomized to receive stavudine (Zerit) and half were randomized to receive a stavudine placebo. Before randomization, patients were stratified according to their antiretroviral treatment history, baseline viral load, and baseline CD4+ cell count. Patients were permitted to intensify their treatment by adding two new NRTIs or NNRTIs to their regimen after 12 weeks of assigned therapy.

In the ritonavir/saquinavir group, 87 (24%) patients remained on randomized treatment throughout 96 weeks, 46% intensified treatment after a median of 25 weeks, and 30% prematurely discontinued study medication at some point during the 96 weeks of follow-up. In the ritonavir/saquinavir/stavudine group, 88 (60%) remained on randomized treatment, 7% intensified treatment after a median of 41 weeks, and 33% prematurely discontinued study medication.

Following treatment, no significant differences were observed in terms of viral suppression or immune recovery. HIV-RNA levels were 1.9 $\log_{10}$ copies/ml below baseline at week 48 in the ritonavir/saquinavir group (85% had HIV-RNA levels below 400 copies/mL at week 48) and 2.1 $\log_{10}$ copies/ml in the ritonavir/saquinavir/stavudine group (91% had HIV-RNA levels below 400 copies/mL), with no statistically significant dif-

ferences between the two groups. Median increases in CD4+ counts between week 0 and week 48 were 160 cells/mm³ and 180 cells/mm³ for the ritonavir/saquinavir and ritonavir/saquinavir/stavudine groups respectively.

Lipodystrophy was reported in 29/175 (17%) evaluable patients during 96 weeks of follow-up. Overall, it was reported significantly more frequently in patients who were randomized to ritonavir/saquinavir/stavudine (22/88 [25%]), than in patients randomized to ritonavir/saquinavir alone (7/87 [8%]). When the analysis was limited to patients without any prior antiretroviral experience, lipodystrophy likewise was significantly more frequent in patients randomized to ritonavir/saquinavir/stavudine (12/50 [24%]) than in those randomized to ritonavir/saquinavir (2/44 [5%]).

The Kaletra Monotherapy Trial

WHILE NOT SPECIFICALLY DISCUSSED BY DR. STASZEWSKI, A BOOSTED PROTEASE inhibitor "monotherapy" study that caused quite a stir within the ranks was reported at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, held in September 2003 (Gathe, 2003). This study enrolled 30 antiretroviral-naive patients—with a mean CD4+ count of 169 cells/mm³ and a mean viral load of 262,020 copies/mL—to receive three lopinavir/ritonavir capsules twice a day (four capsules BID for patients weighing more than 154 pounds).

After 24 weeks, eight patients had discontinued therapy (two were lost to follow-up, two dropped out because of adverse events, one patient was deported, one was non-adherent, one had concomitant hepatitis B infection, and one experienced virologic failure). Among the 22 patients who completed 24 weeks of therapy, 21 (95.4%) had HIV-RNA levels below 400 copies/mL. The one patient with virologic failure had a viral load of 1,510 copies/mL at week 24. Upon conducting genotyping in this patient, the L63P mutation in HIV protease was documented. However, phenotypic testing demonstrated the virus to be completely sensitive to lopinavir/ritonavir.

The mean CD4 count increase at week 24 was 219 cells/mm³ and the investigators reported that adverse events were minimal and the treatment was well tolerated among those completing 24 weeks of treatment.

Additional data from this study are very much anticipated.

Double-Boosted Protease Inhibitor Studies

ACCORDING TO DR. STASZEWSKI, MANY CLINICIANS ARE PRESCRIBING double-boosted protease inhibitors to maximize the effects of therapy, particularly for their treatment-experienced patients. Double-boosted protease inhibitors can, of course, be used in combination with NRTIs and NNRTIs. Such regimens might also be used as NRTI- and NNRTI-sparing regimens. "I found this to be a very important concept after hearing about the potential interactions between ribavirin for the treatment of HCV and various nucleoside analogues used for the treatment of HIV," Dr. Staszewski said. "So I think that double-boosted protease inhibitors could be an alternative to conventional treatment when you have coinfected patients that you want to treat with a hepatitis C regimen."

For patients who are treatment experienced and, perhaps, have high-level resistance to the available NRTIs and NNRTIs, Dr. Staszewski indicated that double-boosted protease inhibitors may have potential, particularly when they are combined with enfuvirtide (Fuzeon). "We know that it's important to use Fuzeon in combination with other drugs that remain active against HIV," he explained. "This doesn't necessarily mean combining it with NRTIs. Double-boosted protease inhibitors may qualify in this situation."

The Fundación Huésped Study

TO EVALUATE THE EFFICACY AND SAFETY OF DOUBLE-BOOSTED PROTEASE INhibitor regimens in heavily pre-treated HIV-infected patients, Dr. Carlos Zala and his colleagues at the Fundación Huésped in Buenos Aires conducted an open-label observational cohort study of patients receiving lopinavir/ritonavir plus either amprenavir or saquinavir and a backbone of NRTIs or NNRTIs (selected based on treatment history) (Zala, 2002). All patients took three lopinavir/ritonavir capsules twice a day (four capsules twice a day if an NNRTI was also used). The amprenavir dose employed was 750 mg BID and the saquinavir dose employed was 1,000 mg BID.

Between July 2000 and January 2001, 42 patients—eight of whom were women—enrolled in the cohort. Nineteen patients received lopinavir/ritonavir/amprenavir and 23 received lopinavir/ritonavir/saquinavir. The median viral load at baseline was 5.55 $\log_{10}$ copies/mL and the median baseline CD4+ count was 93 cells/mm³. On average, the 42 patients had been on three protease inhibitors in the past.

By June 2001, one patient in the saquinavir group died from complications of lymphoma. Seven patients—three in the amprenavir group and four in the saquinavir group—discontinued therapy due to gastrointestinal intolerance and/or poor adherence.

At the time of Dr. Zala's presentation at the 14th International AIDS Conference, held in 2002 in Barcelona, 25 patients had completed 48 weeks of treatment. The median viral load decline from baseline was 3.0 $\log_{10}$ copies/mL. Approximately 80% of evaluable patients had viral load reductions from baseline greater than 1 $\log_{10}$ copies/mL (7/10 patients in the amprenavir group and 13/15 patients in the saquinavir group). As for rates of undetectable viral loads, 31% of the entire group had HIV-RNA levels below 500 copies/mL after 48 weeks, which included 21% of patients in the amprenavir group and 39% of patients in the saquinavir group.

"The study authors were happy with these results, given that they were able to prescribe a double-boosted protease inhibitor regimen that worked for a number of their heavily treatment experienced patients," Dr. Staszewski said. "However, it was clear that patients taking lopinavir, ritonavir, and saquinavir did better than those taking lopinavir, ritonavir, and amprenavir. While they didn't know why these differences were seen, some pharmacokinetic data might explain things."

Pharmacokinetic Considerations

THERE HAVE BEEN A NUMBER OF STUDIES DEMONSTRATING THAT lopinavir and amprenavir appear to be poor antiretroviral partners. In studies reviewed by Dr. Staszewski, the combination of amprenavir and lopinavir/ritonavir resulted in reduced plasma concentrations of lopinavir relative to the usual lopinavir/ritonavir pharmacokinetics and reduced plasma concentrations of amprenavir relative to the usual amprenavir/ritonavir pharmacokinetics (although amprenavir concentrations were elevated relative to amprenavir 1200 mg BID). Data presented at the 11th CROI, held in San Francisco in February, also indicate that fosamprenavir (Lexiva) and lopinavir concentrations are reduced when coadministered, both with ritonavir (Wire, 2004). "So," Dr. Staszewski commented, "it seems that there is a drug interaction between lopinavir/ritonavir and amprenavir, reducing the exposure of the drugs. This might explain why boosted lopinavir and amprenavir didn't

perform as well as boosted lopinavir and saquinavir."

The fact is, combining two protease inhibitors—with ritonavir as a potential booster—can be extremely tricky. While ritonavir may inhibit the metabolism of one protease inhibitor, this could in turn induce the metabolism of the other protease inhibitor prescribed. "When we combine two protease inhibitors with ritonavir, we have a number of interactions to consider," Dr. Staszewski pointed out. "These interactions may be very unpredictable. You have an interaction between protease inhibitor one and protease inhibitor two. And the interactions may inhibit or induce cytochrome P450. And you also have interaction between ritonavir and protease inhibitor one and/or protease inhibitor two and vice versa. So it's really important to evaluate the pharmacokinetics data carefully, and we should not combine two protease inhibitors with ritonavir without knowing the interactions. Otherwise, you run the danger of doing the exact opposite of what you want."

What about lopinavir/ritonavir/saquinavir? To evaluate this particular combination, Dr. Staszewski's group, under the direction of Dr. Christoph Stephan, conducted an analysis of the PK interactions of these three drugs in a prospective, open-label, observational trial (Stephan, 2003). The first group consisted of patients receiving lopinavir/ritonavir (400 mg/100 mg BID) and saquinavir (Invirase, 1000 mg BID) without NRTIs. The second group consisted of patients receiving ritonavir (100 mg BID) and saquinavir (1000 mg BID) without lopinavir, but with two or three NRTIs.

Data were collected from 45 patients in the lopinavir/ritonavir/saquinavir group and 32 patients in the ritonavir/saquinavir group. There was no significant difference between the groups in terms of median saquinavir C_{min}, C_{max}, and AUC. However, median ritonavir C_{min}, C_{max} and AUC were statistically significantly lower in the lopinavir/ritonavir/saquinavir group than in the ritonavir/saquinavir group. Lopinavir levels were comparable to those previously published data.

"What we found was that, in the double-boosted PI regimen of saquinavir, lopinavir, and ritonavir, ritonavir plasma levels were lower than in the ritonavir/saquinavir regimen," Dr. Staszewski explained. "However, the low ritonavir plasma levels were effective in terms of boosting both lopinavir and saquinavir. This study did not show a disadvantageous PK interaction with either saquinavir or lopinavir, indicating that lopinavir, ritonavir, and saquinavir may be combined without dose adjustments."

The LOPSAQ Study

TO PUT THE RITONAVIR-BOOSTED DOUBLE PROTEASE INHIBITOR REGIMEN of lopinavir and saquinavir to the test, Dr. Staszewski and his colleagues began the LOPSAQ (lopinavir/saquinavir) study (Staszewski, 2003a). The regimen was tested in 121 HIV-positive patients with extensive prior treatment experience who had no NRTI options available because of resistance or toxicity. No additional antiretrovirals were used. "This was a population of patients in which we really didn't have many treatment choices," Dr. Staszewski said. "These patients couldn't use and weren't going to benefit from regimens that contained NRTIs, so we wanted to evaluate their responses to a protease inhibitor-only regimen."

Upon entering the study, virus from each of the patients was genotyped. With the genotype results in hand, Dr. Staszewski's team divided the participants into two groups. The first group, consisting of patients who did not have any evidence of protease inhibitor-resistance mutations, switched off their old regimen and were put on a combination consisting of lopinavir/ritonavir (400 mg/100 mg BID) and saquinavir (1000 mg BID). The second group, consisting of patients who harbored virus with evidence of protease inhibitor-resistant virus, initiated a treatment interruption in order to let wild-type (drug-sensitive) virus reemerge. They were then placed on lopinavir/ritonavir and saquinavir.

As explained by Dr. Staszewski, 64 patients were put into the first group and 38 initiated a treatment interruption. During his PRN presentation—using data reported at the 2nd International AIDS Society Conference on HIV and Pathogenesis, held in Paris in 2003—Dr. Staszewski focused on the 64 patients enrolled in the first group.

Thirteen of the 64 (20%) patients were women. The median CD4+ count upon starting the boosted double-protease inhibitor regimen was 168 cells/mm^3; the median viral load was 5.2 $\log_{10}$ copies/mL. Twenty-five of the 64 (39%) enrolled in LOPSAQ because of NRTI toxicity reasons, 37 (58%) enrolled because of resistance to NRTIs, and two (3%) enrolled in LOPSAQ for both reasons.

The median time on antiretroviral therapy, prior to enrolling in the LOPSAQ study, was 6.7 years. The median number of drugs tried in the past was nine and the median number of drug regimens utilized was four. Thirty-two (50%) had been on saquinavir in the past and 16 (25%) had been on lopinavir/ritonavir in the past.

While an undetectable viral load is always the ultimate goal of any antiretroviral drug regimen, this may be a tough order to fill in heavily treatment-experienced patients. Consequently, Dr. Staszewski's group defined virologic success by stratifying patients according to baseline viral load. For example, patients who entered the study with a viral load below 400 copies/mL would require a viral load below 400 copies/mL after 24 weeks of treatment to be considered a success. For patients with baseline viral loads of 400 to 100,000 copies/mL, virologic success would be considered a viral load below 400 copies/mL after 24 weeks of therapy. And for patients with baseline viral loads above 100,000 copies/mL, virologic success would be considered a viral load below 10,000 copies/mL after 24 weeks of treatment.

Forty-five (70.3%) of the 64 evaluable patients were considered virologic responders after 24 weeks of treatment. Viral load dropped, on average, by 3 $\log_{10}$ copies/mL after 24 weeks, yielding a median viral load of 210 copies/mL in the intent-to-treat analysis (137 copies/mL in the as-treated analysis). The median CD4+ count was approximately 300 cells/mm^3 after 24 weeks of treatment, in both the intent-to-treat and as-treated analyses. "These are very good results and we have 48-week data indicating similar viral load reductions and CD4+ cell count increases," Dr. Staszewski said. "We're also seeing good retention in this study. 80% of patients enrolled into this study are still on therapy. We've had seven discontinuations because of virologic failure, four discontinuations because of toxicities, and one death, which was not HIV related. In fact, we haven't had any CDC AIDS-defining events in the study."

As for factors related to achieving a virologic response, a number of univariate analyses were performed. Nonresponders had a median viral load of 4.95 $\log_{10}$ copies/mL at the end of their last failing regimen, whereas responders had a median baseline viral load of 3.45 $\log_{10}$ copies/mL. However, there was no statistically significant difference between responders and nonresponders with respect to baseline viral loads documented by the LOPSAQ study team. CD4+ cell counts were significantly higher, both at the end of the patients' last failing regimen and at baseline, in responders versus nonresponders (667 vs. 112 cells/mm^3 at the end of their last failing regimen and 96 vs. 67 cells/mm^3 at baseline).

Other factors related to virologic responses included the number of drugs previously taken. Responders had taken a median of eight drugs in the past, compared to a median of 12 drugs among nonresponders. Not surprisingly, patients with the most protease inhibitor experience

were least likely to respond. Responders had a median of two protease inhibitors behind them, whereas nonresponders had tried a median of four protease inhibitors in the past. Similarly, 88% and 44% of nonresponders had tried either saquinavir or lopinavir/ritonavir in the past, compared to 36% and 18% of responders respectively. Nonresponders were also more likely to have taken amprenavir in the past as well (39% vs. 11% respectively).

In a pharmacokinetic substudy of the LOPSAQ trial, Dr. Staszewski's group found that there was substantial heterogeneity in plasma levels among participants. Plasma concentrations tended to be lower in nonresponders than in responders. The AUC and C_{min} of saquinavir was 47% and 50% lower, respectively, and the AUC and C_{min} of lopinavir was 22% and 32% lower in nonresponders than responders, although these PK differences did not reach statistical significance.

"For patients with protease inhibitor-sensitive HIV who are not able to take NRTIs, for reasons of resistance or toxicity, an NRTI-sparing boosted double protease inhibitor regimen may be a potential option," Dr. Staszewski said in reviewing the LOPSAQ data. "We saw poorer results in patients with heavy protease inhibitor pretreatment, high viral loads, low CD4+ cell counts, and more than eight protease inhibitor-resistant mutations. However, in patients such as this, the potential usefulness of enfuvirtide (Fuzeon) should not be ignored."

New and Noteworthy

A HANDFUL OF PHARMACOKINETIC STUDIES EVALUATING TRIPLE-PROTEASE inhibitor regimens were reported at the 11th CROI. In one study reported by investigators at Chelsea and Westminster Hospital in London, the steady-state pharmacokinetics of 300 mg atazanavir (Reyataz), 1,600 mg saquinavir (Invirase), and 100 mg ritonavir—all administered once a day—were evaluated (Boffito, 2004). The addition of atazanavir to saquinavir/ritonavir resulted in a significant increase in the saquinavir trough, C_{max}, and AUC (by 112%, 42%, and 60% respectively), with a slight increase in the saquinavir half-life (17%). The ritonavir C_{max} and AUC increased significantly with atazanavir administration (by 34% and 41% respectively). As for atazanavir levels, these were comparable to those documented previously in patients receiving atazanavir/ritonavir without saquinavir. Based on these data, the study authors recommend that once-daily administration of atazanavir, saquinavir, and ritonavir—using the doses specified above—should be considered for further clinical evaluation.

In another study reported by the same research team, the steady-state pharmacokinetics of 1,000 mg saquinavir, 700 mg fosamprenavir, and either 100 mg or 200 mg ritonavir—all administered twice a day—were evaluated in 18 HIV-infected patients (Boffito, 2004a). Accordingly, the coadministration of fosamprenavir dosed at 700 mg BID with saquinavir and ritonavir (100 mg BID) resulted in a statistically insignificant decrease in the saquinavir AUC, trough, and C_{max} (–14%, –24%, and –9% respectively), but this was compensated for by the 200 mg BID ritonavir dose, which resulted in statistically insignificant increases in the saquinavir AUC, trough, and C_{max} (12%, 3%, and 20% respectively). Fosamprenavir levels did not appear to be significantly influenced by saquinavir coadministration. A 54% decrease from baseline in the ritonavir trough was observed with the addition of fosamprenavir to saquinavir/ritonavir. On the basis of these results, a possible dose combination for further exploration could be 1,000 mg saquinavir, 700 mg fosamprenavir, and 200 mg ritonavir, administered twice daily. *prn*

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