From Concept to Care: Pharmacokinetic Boosting of Protease Inhibitors

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PROTEASE INHIBITORS HAVE PLAYED AN INSTRUMENTAL ROLE IN decreasing mortality and morbidity among people with HIV infection. At the same time, this class of antiretrovirals has been associated with a number of disadvantages. 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 a variety of metabolic complications. Third, cross-resistance remains a central concern; a simple switch from one protease inhibitor to another—if protease mutations are documented—often yields lackluster results.

Fortunately, extensive data generated over the past several years have shed more encouraging light on the utility of protease inhibitors in the treatment of HIV infection. Pharmacokinetic "boosting"—primarily 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 with respect to the use of two protease inhibitors—both boosted using low-dose ritonavir—as a therapeutic option. These double-boosted protease inhibitor combinations appear to hold a great deal of promise, particularly for patients who have tried and failed protease inhibitor therapy in the past.

Boosting: Pharmacokinetic Principles

THE NEED TO IMPROVE BOTH THE CONVENIENCE AND EFFECTIVENESS OF protease inhibitors has led to research focusing on pharmacologic enhancement. Ritonavir is an ideal pharmacologic enhancer because it inhibits two key stages of metabolism. First, it inhibits what is known as first-pass metabolism, which occurs during absorption. Enterocytes that line the intestine contain both CYP3A4, one of the key cytochrome P450 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 plasma 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.

Ritonavir's interactions with other drugs are complex and involve an understanding of pharmacology that extends beyond the cytochrome P450 system. This is reviewed in detail in "XEN and the Art of Pharmacology: New Learning from an Old Science," beginning on page 10, and was also touched upon by Dr. Boffito. In one series of studies reviewed by Dr. Boffito, researchers at Vanderbilt University School of Medicine evaluated the activation of orphan nuclear receptors—proteins responsible for increased transcription of the CYP3A4 gene, including pregnane X receptor (PXR)—by different protease inhibitors (Marzolini, 2004). At the

11th Conference on Retroviruses and Opportunistic Infections (CROI), it was demonstrated that the protease inhibitors, used alone or in combination, had varied effects on these proteins. The protease inhibitors (fos)amprenavir (Agenerase; Lexiva), nelfinavir (Viracept), lopinavir (without ritonavir), and ritonavir (Norvir) are PXR substrates. When these protease inhibitors were combined with rifampicin, another PXR substrate and a well-known inducer, the extent of the maximal CYP3A4 transcriptional activity (CYP3A4 synthesis) was less than in the presence of rifampicin alone. Similar findings were observed when ritonavir was combined with lopinavir, suggesting that the protease inhibitors tested are partial agonists of PXR. "Interestingly," Dr. Boffito commented, "the three-protease inhibitor combination of lopinavir, ritonavir, and amprenavir appeared to have a synergistic effect on PXR. This may explain the low plasma concentrations of lopinavir and amprenavir seen in clinical trials evaluating this combination."

In discussing various boosting strategies, Dr. Boffito pointed out that the pharmacologic enhancement achieved using ritonavir depends on the coadministered protease inhibitor being used. With saquinavir (Invirase; Fortovase) and lopinavir, for example, ritonavir's most notable effect is a boost to the C_{max}. "This suggests that the effect of ritonavir on saquinavir is exerted at the absorption level and during first-pass metabolism," Dr. Boffito explained. With indinavir (Crixivan) and (fos)amprenavir, ritonavir coadministration allows for prolongation of their half-lives. "With these drugs, ritonavir exerts its effects mainly on CYP3A4 clearance at the liver level," she added. "We see a limited increase in the indinavir or amprenavir C_{max} when using ritonavir to boost these drugs. What changes is the elimination half-life and, therefore, an increase in the C_{trough}."

Boosting: Pharmacodynamic Principles

THE PHARMACOKINETIC BENEFITS OF RITONAVIR BOOSTING ARE ONLY ONE part of the equation. It is also important to understand the pharmacodynamic benefits as well. "We want to achieve high enough plasma concentrations for a reason," Dr. Boffito said. "We need protease inhibitor concentrations to be high enough to inhibit HIV replication. If this doesn't happen, HIV continues to replicate and contributes to resistance. And when we're dealing with HIV strains that have become resistant to antiretroviral therapy, we need more drug to inhibit replication. At the same time, we cannot increase the concentrations to an extended limit, as this would be associated with toxicity" (see Figure 1 on page 16).

An initial evaluation of the potential pharmacodynamic benefits of ritonavir boosting was published by Dr. John Condra and his colleagues at Merck Laboratories (Condra, 2000). Most protease inhibitors maintain *in vivo* $C_{troughs}$ above their IC_{95} values for wild-type HIV. However, these $C_{troughs}$ are well below corrected IC_{95} values for protease inhibitor-resis-
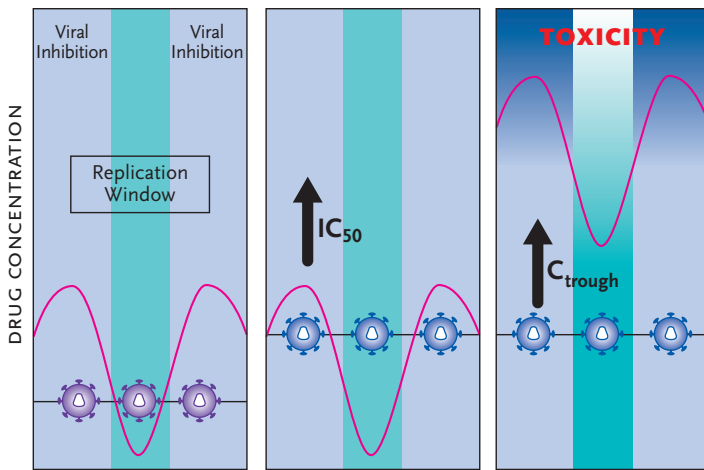
FIGURE 1. **Establishing Optimal Antiretroviral Plasma Levels**

Dosing antiretroviral therapy, particularly in the context of either delaying or overcoming drug resistance, requires an understanding of basic pharmacology principles. For example, protease inhibitor concentrations in blood plasma must be high enough to inhibit HIV replication. If plasma concentrations are not high enough, HIV continues to replicate and contributes to drug resistance. When dealing with HIV mutants that have become resistant to antiretroviral therapy, there is the possibility of increasing drug concentrations to once again inhibit viral replication. However, concentrations cannot be increased to an extended limit, as this would be associated with toxicity. The key, then, is to maintain drug concentrations—including the C_{max} and C_{trough}—above the minimum effective concentration and below the maximum safe concentration, a difficult task in the absence of clearly defined pharmacokinetic cutoffs.

Source: Marta Boffito, MD, PhD
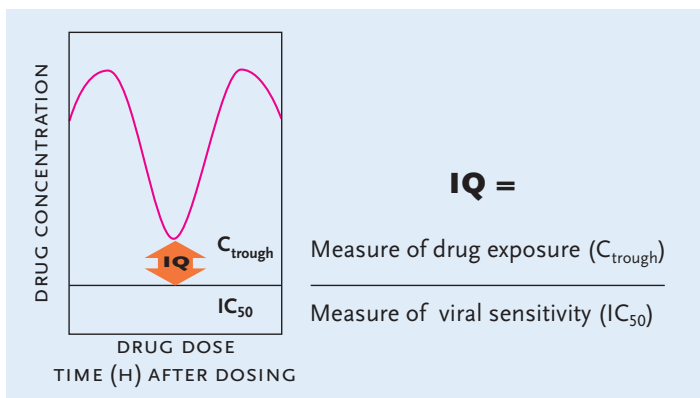
FIGURE 2. **Inhibitory Quotient**

The inhibitory quotient (IQ) is expressed as a drug's C_{trough}, determined using therapeutic drug monitoring, over that of the *in vitro* IC_{50} (or IC_{95}) of both wild-type and mutant virus, determined using phenotypic assays (i.e., IQ = C_{trough}/IC_{50}). In essence, the IQ is a buffer zone between drug concentrations that are active against drug-resistant or wild-type virus and drug concentrations that allow for the emergence of drug-resistance mutants. However, before IQ can be studied further and eventually incorporated into the routine care of HIV-positive patients receiving antiretroviral therapy, consensus is required with respect to the issue of protein binding. Many antiretrovirals are bound to proteins in blood plasma, thereby limiting the actual concentration of free drug. Experts in the field of HIV pharmacology have yet to determine the optimum way of adjusting IQs for protein binding.

Source: Marta Boffito, MD, PhD

tant viruses from patients experiencing virologic failure of indinavir and/or nelfinavir. Compounded by the cross-resistance that exists between these agents, these pharmacokinetic data suggested that none of the single protease inhibitors available in 2000 would have been effective in many patients with a history of protease inhibitor failure. However, as was documented in this paper, saquinavir, amprenavir, and indinavir blood levels were increased substantially when each was coadministered with ritonavir, with 12-hour $C_{troughs}$ exceeding corrected wild-type IC_{95} by twofold, sevenfold, and 28–79-fold respectively. These indinavir and amprenavir $C_{troughs}$ exceeded the $IC_{95}s$ for most protease inhibitor-resistant viruses tested, a finding that paved the way for additional research evaluating the benefits of ritonavir boosting in patients with protease inhibitor-resistant virus.

"When we look at a concentration-effect curve and see resistant virus that has developed lower susceptibility to a given drug, it becomes clear that we need high concentrations to inhibit the replication of these viruses," Dr. Boffito explained. "This is why clinical pharmacologists developed the pharmacokinetic/pharmacodynamic parameter called IQ: the inhibitory quotient."

The inhibitory quotient (IQ) is expressed as the actual C_{trough} over that of the *in vitro* IC_{50} (or IC_{95}) of both wild-type and mutant virus, determined using phenotypic assays (i.e., IQ = C_{trough}/IC_{50}). In essence, the IQ is a buffer zone between drug concentrations that are active against drug-resistant or wild-type virus and drug concentrations that allow for the emergence of drug-resistance mutants (see Figure 2). Consequently, drugs with the lowest IQ are more likely to be associated with poor virologic outcome, whereas those with high IQs are more likely to stay on top of—and maintain control of—viral replication. "This parameter would be extremely useful to predict drug efficacy using ritonavir-boosted regimens in treatment-experienced patients," Dr. Boffito commented. It is important to note, however, that many drugs are bound to proteins in blood plasma, thereby reducing the effective (free) drug concentrations. In turn, the IC_{50} values used in calculating the IQ need to be adjusted for protein binding. Because these adjustments can be difficult, given a lack of standardization, the utility of the IQ is still largely theoretical.

Double-Boosted Protease Inhibitors

DR. BOFFITO MOVED ON TO THE TOPIC OF DOUBLE-BOOSTED PROTEASE inhibitors—that is, the use of low-dose ritonavir to boost the concentrations of two coadministered protease inhibitors being used at therapeutic doses (see Figure 3). *In vitro* studies have suggested synergistic anti-HIV activity using combinations of protease inhibitors and clinical trials have demonstrated the benefit of using two protease inhibitors in treatment-experienced patients. While double-boosted protease inhibitors can be used in combination with NRTIs and NNRTIs, there is also the possibility of using them as NRTI- and NNRTI-sparing regimens. "This may be useful in patients that harbor strains of HIV resistant to RTIs or, perhaps, patients who cannot continue on RTIs because of toxicity reasons," Dr. Boffito said.

A number of pharmacokinetic studies involving double-boosted protease inhibitors have been conducted. Table 1 reviews the doses used in these studies, along with notes regarding the use of therapeutic drug monitoring (TDM) to best utilize the coadministration of two protease inhibitors with low-dose ritonavir.
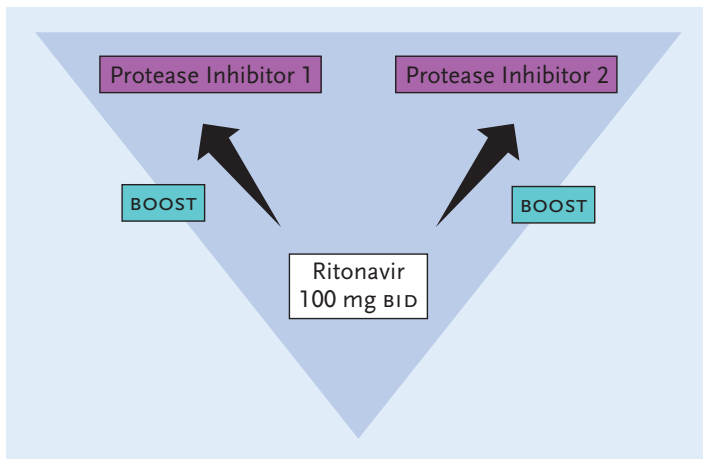
FIGURE 3. Double Protease Inhibitor Boosting

Generally speaking, "double-boosted protease inhibitors" refers to the use of low-dose ritonavir to boost the concentrations of two coadministered protease inhibitors being used at therapeutic doses. *In vitro* studies have suggested synergistic anti-HIV activity using combinations of protease inhibitors and clinical trials have demonstrated the benefit of using two protease inhibitors in treatment-experienced patients. While double-boosted protease inhibitors can be used in combination with NRTIs and NNRTIs, there is also the possibility of using them as NRTI- and NNRTI-sparing regimens. This may be useful in patients harboring HIV mutants resistant to RTIs or for patients who cannot continue on RTIs because of toxicity reasons.

Source: Marta Boffito, MD, PhD

The LOPSAQ Study

ONE DOUBLE-BOOSTED PROTEASE INHIBITOR REGIMEN REVIEWED BY Dr. Boffito involves lopinavir and saquinavir boosted with low-dose ritonavir. To evaluate the pharmacokinetics of this combination, Dr. Christoph Stephan and his colleagues of the Frankfurt HIV Cohort study conducted an analysis of the potential three-way interactions in a prospective, open-label, observational trial (Stephan, 2004). One study group consisted of patients receiving lopinavir/ritonavir (400 mg/100 mg BID) and saquinavir (1000 mg BID) without NRTIs. A second group consisted of patients receiving ritonavir (100 mg BID) and saquinavir (1000 mg BID), without lopinavir, but with two or three NRTIs.

Pharmacokinetics data were collected from 45 patients in the saquinavir/lopinavir/ritonavir group and 32 patients in the saquinavir/ritonavir group. There were no significant differences between the groups in terms of median saquinavir C_{mins}, C_{maxs}, and AUCs. However, the median ritonavir C_{min}, C_{max}, and AUC were significantly lower in the saquinavir and lopinavir/ritonavir group than in the saquinavir and ritonavir group, suggesting a possible induction of ritonavir metabolism by lopinavir. Lopinavir levels were comparable to those documented in previously published data.

Efficacy data involving this combination are also available, through the Frankfurt HIV Cohort LOPSAQ (lopinavir/saquinavir) study (Staszewski, 2004). It has been tested in 163 HIV-positive patients with extensive prior treatment experience who had few or no NRTI options available because of resistance or toxicity and, thus, only took the double-boosted protease inhibitors while participating in the trial. One-hundred twenty-six patients had been followed for at least 48 weeks by the time these data were presented at the XV International AIDS Conference in Bangkok in July.

Upon entering the study, virus from patients with detectable viral load was genotyped. The participants were then divided into two groups. In the first group, patients who did not have any evidence of protease inhibitor-resistance mutations were switched off their old regimen and put on the saquinavir and lopinavir/ritonavir combination. In the second group, patients who either harbored virus with evidence or protease inhibitor-resistant virus or had systemic toxicity initiated a treatment interruption in order to let wild-type (drug-sensitive) virus reemerge or to let side-effect symptoms resolve. They were then placed on saquinavir and lopinavir/ritonavir.

Eighty-eight patients initiated a treatment interruption prior to starting saquinavir and lopinavir/ritonavir.

The median CD4+ count upon starting the boosted double-protease inhibitor regimen was 165 cells/mm³; the median viral load was 5.2 $\log_{10}$ copies/mL. The median time on antiretroviral therapy, prior to enrolling in the LOPSAQ study, was 6.3 years. The median number of protease inhibitors tried in the past was three.

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. In turn, the LOPSAQ study investigators defined virologic success by stratifying patients according to baseline viral load. For example, patients who entered the study with a viral load below 10,000 copies/mL would need a viral load below 400 copies/mL after 48 weeks of treatment to be considered a success. For

TABLE 1. Double-Boosted Protease Inhibitor Regimens: Doses Evaluated in PK Trials

Protease Inhibitors	Doses	Therapeutic Drug Monitoring
Saquinavir, lopinavir and ritonavir	1,000 mg, 400 mg, 100 mg BID	Not required for both saquinavir and lopinavir
Saquinavir, amprenavir and ritonavir	1,400 mg, 600 mg, 100 mg BID	May be useful to confirm therapeutic concentrations of saquinavir and amprenavir
Amprenavir, lopinavir and ritonavir	750 mg, 533 mg, 133 mg BID	TDM of both lopinavir and amprenavir required
Fosamprenavir, lopinavir and ritonavir	700 mg, 533 mg, 133 mg BID or 750 mg, 400 mg, 200 mg BID	TDM of both lopinavir and amprenavir required
Nelfinavir, lopinavir and ritonavir	1,250 mg, 533 mg, 133 mg BID	TDM of lopinavir required
Saquinavir, atazanavir and ritonavir	1,600 mg, 300 mg, 100 mg QD	TDM not required? Possible need for ritonavir TDM?
Indinavir, lopinavir and ritonavir	600 mg, 400 mg, 100 mg BID	Not required for both lopinavir and indinavir

Source: Marta Boffito, MD, PhD

patients with baseline viral loads greater than 100,000 copies/mL, virologic success would be considered a 48-week viral load below 10,000 copies/mL.

At week 48, 67 (53.2%) of patients were still on therapy. Thirty-seven patients discontinued because of intolerance, 18 discontinued because of virologic failure, and four discontinued because of the high pill burden. Eleven patients discontinued therapy within days of beginning this regimen, thus they were not included in the 48-week analysis, leaving 115 total evaluable patients.

In the intent-to-treat analysis, viral load dropped, on average, by 2.7 $\log_{10}$ copies/mL and CD4+ counts increased, on average, by 99 cells/mm³. Overall, 77 (61%) patients were considered therapeutic responders, with viral loads between <20 copies/mL and 4,300 copies/mL, after 48 weeks of follow-up. Among the 38 virologic nonresponders, 28 had increased CD4+ cell counts after 48 weeks. The median CD4+ count among all nonresponders was 155 cells/mm³—an increase of 56.5 cells/mm³ over baseline.

In a pharmacokinetic substudy of the LOPSAQ trial, higher saquinavir concentrations were found to be predictive of clinical responses in these treatment-experienced patients (Staszewski, 2004a). Data from fifty-six patients were included in this substudy. Twenty of the patients were virologic nonresponders and 36 were virologic responders. Plasma concentrations were lower in nonresponders than in responders. The AUC, C_{min} and C_{max} of saquinavir were 37%, 49%, and 27% significantly lower respectively, and the AUC and C_{min} of lopinavir were 28% and 29% lower in nonresponders than responders, although these pharmacokinetic differences did not reach statistical significance. Ritonavir C_{mins} were also significantly reduced in nonresponders by 53%.

Double-Boosting at Chelsea and Westminster Hospital

DR. BOFFITO DISCUSSED SOME OF HER OWN DOUBLE-BOOSTING PHARMA-cokinetics work at Chelsea and Westminster Hospital, focusing on a pair of studies that were both initially reported at the 11th CROI in February in San Francisco.

In the first study, 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 C_{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, Dr. Boffito's group recommended that once-daily administration of atazanavir, saquinavir, and ritonavir—using the doses specified above—should be evaluated further in clinical trials.

In the second study, 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 nonsignificant decrease in the saquinavir AUC, C_{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, C_{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 C_{trough} was observed with addition of fosamprenavir to saquinavir/ritonavir. "Here, with the use of 200 mg of ritonavir, we appeared to have enough of a boost to achieve sufficient saquinavir and fosamprenavir concentrations."

A Tricky Mix: Lopinavir, Ritonavir, and Fosamprenavir

WHILE A NUMBER OF REGIMENS CONSISTING OF TWO PROTEASE inhibitors plus low-dose ritonavir have been deemed to have acceptable pharmacokinetic profiles, regimens consisting of lopinavir, ritonavir, and amprenavir/fosamprenavir have been shown to be problematic. Fosamprenavir—the phosphate ester prodrug of amprenavir—lopinavir, and ritonavir are inhibitors and inducers of CYP3A4. All three protease inhibitors are also substrates for P-glycoprotein and have P-glycoprotein induction or inhibition properties. Data from an AIDS Clinical Trials Group (ACTG A5143)-sponsored study concluded that the combination of fosamprenavir, lopinavir, and ritonavir results in marked reductions in plasma concentrations of amprenavir and lopinavir (Kashuba, 2003). In turn, additional studies have been conducted to assess potential interventions to overcome this pharmacokinetic interaction.

In a report at the 11th CROI detailing two studies, revised doses of lopinavir and fosamprenavir were compared to the typical doses—and plasma concentrations—of ritonavir-boosted fosamprenavir and ritonavir-boosted lopinavir (Wire, 2004). The first study evaluated 1,400 mg fosamprenavir with 533/133 mg of lopinavir/ritonavir, all taken twice a day. The second study evaluated 1,400 mg fosamprenavir plus 400/100 mg of lopinavir/ritonavir, with an additional 100 mg of ritonavir, all taken twice a day.

Amprenavir levels remained significantly lower, compared to ritonavir-boosted fosamprenavir (in the absence of lopinavir). Increasing the fosamprenavir dose to 1,400 mg BID resulted in higher amprenavir concentrations than adding extra ritonavir. In fact, adding extra ritonavir had a significant negative impact on amprenavir concentrations.

Increasing the lopinavir/ritonavir dose to 533/133 mg BID maintained lopinavir concentrations. Adding extra ritonavir increased lopinavir levels 30% to 40%.

It is also worth noting that, of the 36 HIV-negative volunteers enrolled into each study, only 23 completed the first study and 20 completed the second study. A total of 10 patients in the first study and 13 patients in the second study withdrew because of adverse events.

Investigators have also looked at the possibility of separating the fosamprenavir and lopinavir/ritonavir dosing times, by four hours and by 12 hours (Corbett, 2004). In this study, HIV-negative volunteers were allotted to one of three treatment groups: 1) fosamprenavir (700 mg BID) plus lopinavir/ritonavir (400/100 mg BID) taken simultaneously; 2) fosamprenavir/ritonavir (700/100 mg BID) plus lopinavir ritonavir (400/100 mg BID), taken four fours apart; or 3) fosamprenavir (1,400/200 mg QD) plus lopinavir/ritonavir (800/200 mg QD), 12 hours apart.

Pharmacokinetic sampling found that separating the administration of fosamprenavir and lopinavir/ritonavir, by either four or 12 hours, did not improve the pharmacokinetics of amprenavir. However, lopinavir concentrations did increase when the doses were separated, probably because of the additional ritonavir.

"At this point in time, there's no recommended dosing for fosamprenavir, lopinavir, and ritonavir used in combination," Dr. Boffito said. "Additional studies are necessary to determine how best to work

around the tricky interactions seen with this combination."

While standardized dosing has not yet been determined, data from clinical trials evaluating the efficacy of fosamprenavir and lopinavir/ritonavir in treatment-experienced patients suggest that this combination can be used safely—with the use of therapeutic drug monitoring (TDM). In one study reported at the xv International AIDS Conference, held this past summer in Bangkok, fosamprenavir and lopinavir/ritonavir therapy was initiated in 15 heavily treatment-experienced patients (Bell, 2004). Amprenavir and lopinavir TDM results were available for nine of the 15 patients. Target $C_{troughs}$, for the suppression of wild-type HIV, are 400 and 1,000 ng/mL for amprenavir and lopinavir respectively. $C_{troughs}$ of 1,200 and 4,000 ng/mL have been suggested for drug-resistant HIV strains. Three of the nine patients had an amprenavir C_{trough} greater than 1,200 ng/mL, whereas only one patient had an amprenavir C_{trough} less than 400 ng/mL. Six of nine patients had a lopinavir C_{trough} greater than 4,000 ng/mL, whereas none had a C_{trough} less than 1,000 ng/mL. At least two additional studies have reported similar findings with amprenavir (De Luca, 2004; Wynn Vezina, 2004).

"These studies have shown that some highly-experienced patients do respond well to a regimen consisting of fosamprenavir and lopinavir/ritonavir," Dr. Boffito commented. "However, it's important to stress that therapeutic drug monitoring was used in these studies and is recommended to ensure that C_{trough} values are at least greater than HIV wild-type targets. However, for patients with $C_{troughs}$ that are too low, we do not yet have a recommendation in terms of a dose adjustment."

Conclusion

IN HER CONCLUDING REMARKS, DR. BOFFITO STRESSED THE POTENTIAL importance of TDM, particularly for treatment-experienced patients taking complex combinations of antiretroviral drugs. There's still a need to more clearly define, through research, the who, when, and how of TDM. "Currently," she said, "the guidelines for the treatment of HIV infection do not recommend using TDM in all patients starting antiretroviral therapy. It is only recommended in some difficult, complex situations where this tool has been shown to be beneficial. The problem is that there is a continuous process of defining target levels. The fact is, we do not really know what the target levels really need to be, given that these drugs act inside cells, and TDM measures only plasma concentrations. Forgetting about intracellular concentrations for the moment, we also don't now how much drug we really need in plasma. We don't really know if we need consistent concentrations for the full dosing interval and we don't really know which pharmacokinetic parameter relates best to drug efficacy."

Dr. Boffito also pointed out that more research is needed to better understand the influence of covariables—such as gender, coinfection (e.g., chronic hepatitis C virus infection), and ethnicity—on target levels. Finally, researchers and the pharmaceutical industry need to work together closely to standardize dose-adjustment procedures. "All of the answers to these questions might come from a proper study, such as a randomized, controlled, prospective study investigating the usefulness of TDM," she suggested. "However, we still do not know how feasible it is to perform such a study." *prn*

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