# Perspectives Update on HIV Pharmacology and Therapeutic Drug Monitoring

Pharmacokinetic interactions of antiretroviral drugs and the potential clinical role of therapeutic drug monitoring were discussed by Charles W. Flexner, MD, at the International AIDS Society–USA New York course in March.

The long-term success of an antiretroviral regimen depends on maintaining inhibitory concentrations of active drug at the site of HIV replication sufficient to suppress viral load and prevent viral mutation and resistance. Although HIV inhibitory concentrations can be identified for antiretroviral drugs, there are persistent issues surrounding the use of drug blood concentrations to guide treatment. In general, the higher the trough concentration, the better the inhibition of HIV. However, precise therapeutic concentration ranges have not been identified for any antiretroviral drug. Further, therapeutic drug monitoring may not be necessary if drug pharmacokinetic profiles can be optimized in other ways-eg, by exploiting beneficial pharmacokinetic interactions such as those used to maintain increased blood levels of protease inhibitors. Finally, drug concentrations alone are not the ultimate determinant of treatment outcome; other important factors include tolerability, safety, adherence, treatment history, and resistance profile.

### **Beneficial Drug Interactions**

Protease inhibitor combinations based on the ability of drugs like ritonavir to increase concentrations of the paired drug through pharmacokinetic interactions are increasingly used in treatment. Combinations that exhibit such a beneficial interaction include ritonavir/

Dr Flexner is Associate Professor of Medicine, Pharmacology, and International Health at the Johns Hopkins University in Baltimore, Maryland. saquinavir, ritonavir/indinavir, delavirdine/saquinavir, ritonavir/nelfinavir, nelfinavir/saquinavir, ritonavir/amprenavir, and lopinavir/ritonavir.

The inhibitory quotient has emerged as a way of assessing the relative clinical potency of these combinations, and a high inhibitory quotient has become an important target for newer anti-HIV drugs. The use of the inhibitory quotient is motivated by the predictive value for virologic response of protease inhibitor trough concentrations in some studies. The inhibitory quotient usually is expressed as the drug minimum blood concentration ( $C_{min}$ )

The pharmacokinetic profiles of some dual protease inhibitor regimens support further investigation of once-daily dosing

divided by the HIV 50% inhibitory concentration  $(IC_{50})$  of the drug. The  $IC_{50}$  is often adjusted for protein binding, since drugs that are highly protein bound will have an artifactually low IC<sub>50</sub> in the presence of low concentrations of protein. Caution currently is warranted in the use of publicized inhibitory quotients, since the C<sub>min</sub> and inhibitory concentration values used to derive them vary according to data set used (frequently, according to which drug combination is being touted as superior to another). For reliable inhibitory quotients, comparative data for the different protease inhibitor combinations and other drugs need to be generated under identical experimental conditions.

There is considerable interest in developing protease inhibitor combinations with pharmacokinetic profiles that will permit once-daily dosing. Combinations being considered in this regard include ritonavir/amprenavir, lopinavir/ritonavir, ritonavir/indinavir, and ritonavir/saquinavir. For example, use of amprenavir 1200 mg once daily plus ritonavir 200 mg once daily has been shown to produce trough drug concentrations comparable to those produced by amprenavir 600 mg twice a day plus ritonavir 100 mg twice a day (Wood et al, 5th Cong Drug Ther HIV Infect, 2000). This combination can also be administered with a once-daily dose of the nonnucleoside reverse transcriptase inhibitor (NNRTI) efavirenz, without adverse effect on amprenavir blood levels (Figure 1).

Recent findings, however, indicate that the combination of dual protease inhibitors with NNRTIs may require a ritonavir dose of more than 100 mg twice daily. For example, efavirenz decreased indinavir area under the concentrationtime curve (AUC) by 30% when added to indinavir 800 mg plus ritonavir 100 mg twice daily, and decreased the lopinavir AUC by 19% and  $C_{\mbox{\scriptsize min}}$  by 33% when added to standard-dose lopinavir/ritonavir (400/ 100 mg bid). Therefore it is now recommended that the ritonavir dose be increased to 200 mg twice a day in dual protease inhibitor combinations with efavirenz or nevirapine. The dose of lopinavir should be increased to 4 capsules twice daily (533/133 mg bid) when combined with efavirenz or nevirapine.

The potential advantages to once-daily dosing of antiretroviral regimens include increased convenience, the potential for better overall adherence (in terms of taking a higher proportion of total prescribed doses), and the ability to administer a once-daily regimen as directly observed therapy. There are also potential disadvantages. Once-daily dosing generally produces lower trough drug concentrations than does twice-daily dosing of the same drug at the same daily dose. In addition, the virologic consequences of missing a dose or of late dosing may be worse with a once-daily regimen than with a twice-daily regimen due to lower trough drug levels. The risk of treatment failure or emergence of resistance may be correspondingly increased.

## Drug Concentrations and Toxicity

Focus on the potential advantages of maintaining a potent antiretroviral effect by ensuring high levels of protease inhibitors should not obscure potential toxicity risks. In one recent study, higher indinavir AUC and blood maximum concentration  $(C_{max})$  values were associated with greater risk of nephrotoxicity (eg, kidney stones or flank pain) in patients taking indinavir 800 mg 3 times a day (Burger et al, 8th CROI, 2001). The indinavir  $C_{\mbox{\scriptsize min}}$  values were not associated with nephrotoxicity in this study. In another study, increasing indinavir  $C_{\scriptscriptstyle max}$  and  $C_{\scriptscriptstyle min}$  values were associated with increased incidence of nephrolithiasis, with nephrolithiasis occurring in 0%, 2%, 6%, and 10% of patients receiving indinavir/ritonavir 400/100 mg, 400/400 mg, 600/100 mg, and 800/100 mg twice daily, respectively (Lamotte et al, 8th CROI, 2001). Unpublished data from Miles and colleagues at the University of California Los Angeles have also indicated an association of higher indinavir trough concentrations (>1 µg/mL) with hyper-retinoid syndrome (characterized by acute dry lips, ingrown toenails, and loss of hair on the extremities; S. A. Miles, MD, personal communication). Such findings indicate potential for increased toxicity with higher indinavir concentrations produced by combined administration with ritonavir, and may indicate the need for reducing the dosage of one of the agents in some cases.

## Potential Role for Therapeutic Drug Monitoring

For therapeutic drug monitoring to have a role in antiretroviral therapy, active drug levels must be quantifiable, there must be a quantitative relationship between drug level and outcome of interest (eg, anti-HIV effect or toxicity, for example), and the information should translate into ability to modulate therapy to the patient's benefit. Nucleoside and nucleotide reverse transcriptase inhibitors (nRTIs and ntRTIs) require intracellular phosphorylation to their active form. Although the intracellu-



Figure **1.** Effect of efavirenz administration on amprenavir concentrations with amprenavir plus ritonavir treatment in the National Institutes of Health IRT-023 study. Courtesy of Judith Falloon.

lar half-life for many of these agents is known, and is known to be greater than the plasma half-life of the drug in most cases, the intracellular levels of the active forms currently are very difficult to measure. It is thus generally considered impractical to undertake large-scale studies to evaluate the potential benefit of therapeutic drug monitoring by measuring intracellular drug levels or to monitor serum or plasma levels of nRTIs and ntRTIs.

NNRTIS do not require intracellular activation. Plasma levels of efavirenz, for example, have been shown to correlate with drug activity. Efavirenz has a reasonably wide therapeutic index (ratio of toxic to active drug levels), a long half-life, and a good inhibitory quotient; thus, patients would probably not benefit from having drug levels monitored, since concentrations in nearly all are likely to fall within a range associated with high antiretroviral activity and no substantially increased risk of toxicity.

Therapeutic drug monitoring appears more reasonable for protease inhibitors. These agents are metabolized via the cytochrome P450 system, mainly the 3A4 enzyme, with some agents in the class being cytochrome P450 inducers and some inhibitors. Many other drugs are metabolized via the 3A4 system and thus can affect protease inhibitor metabolism. Among NNRTIs, for example, nevirapine and efavirenz are 3A4 inducers and delavirdine is a 3A4 inhibitor. Further, there is substantial interpatient variation in

metabolism of individual protease inhibitors. Figure 2 shows the relationship of peak viral load reduction to 24-hour AUC for different saquinavir dosages. Higher saquinavir dosages are associated with greater AUC values, and there is a general correlation of low AUC values with lower peak viral load reduction and of higher AUC values with greater peak reduction. However, there is significant spread in the data, such that (1) there is overlap in the range of AUC values between dosages and (2) some patients exhibit low peak viral load reductions at high AUC values and high peak reductions at low AUC values. With such variability, it is unclear whether increasing dosage will result in increased antiretroviral effect or even whether, given variations in metabolism, doubling the dose will double the AUC value in an individual. Intraindividual variability of pharmacokinetics has not been sufficiently defined for most antiretroviral drugs.

For therapeutic drug monitoring to be clinically useful, a number of criteria should be satisfied. Clinical studies should document the therapeutic range or the therapeutic trough concentration of the drug. Plasma concentration should reflect the concentration at the site of drug action. It should also be known that a lack of drug effect is detrimental to the patient. These criteria are only partially satisfied by only some of the available antiretroviral agents. From a laboratory viewpoint, the drug assay for monitoring should (1) be



Figure **2.** Peak viral load reductions and area under the concentration-time curve (AUC) values according to saquinavir soft-gel capsule (SGC) dosage in NV15107 study. Courtesy of Steven A. Miles, MD.

accurate, precise, and specific, (2) require a small sample volume, (3) yield results quickly, and (4) be relatively inexpensive. Although accurate and relatively inexpensive test methods are available, assays cannot be performed with small sample volumes for all antiretroviral drugs. The greatest problem with regard to utility of monitoring from the laboratory perspective is the extended turn-around time for test results, often 2 or 3 weeks or longer.

Clinical study data on the effects of optimizing drug concentrations have begun to accumulate. Figure 3 shows proportions of patients with reduction of viral load to less than 200 HIV-1 RNA copies/mL at 6 months in the VIRADAPT study, according to whether protease inhibitor concentrations were optimal at baseline ( $\geq$ 2 times the  $IC_{95}$ ) and whether viral genotype analysis was available for treatment decisions (Durant et al, AIDS, 2000). The best outcomes were in those patients with both optimal drug concentrations and genotype data. It is difficult, however, to generalize these findings to clinical practice; the low proportions of patients achieving viral suppression overall and the poor outcome in the standard of care group suggest that this patient population was particularly difficult to treat. This was not a therapeutic drug monitoring study; drug doses were not adjusted to produce optimal concentrations.

Additional information on pharmacokinetically-based treatment comes from the PHARMADAPT study, in which 256 treatment-experienced patients were randomized to genotypic analysis or genotypic analysis plus therapeutic drug monitoring. Pharmacokinetic analysis and genotypic analysis were performed at week 4, with modification of treatment being permitted at week 8 on the basis of available information. At 12 weeks, the proportion of patients with plasma HIV-1 RNA level below the limit of detection was not significantly greater in the therapeutic drug monitoring group (43%) compared with the genotype-only group (50%), and no difference was seen between the 2 groups in this regard at week 24 (Clevenbergh et al, 8th CROI, 2001).

The usefulness of these data are in question. The target drug concentrations in the therapeutic drug monitoring group were based on protein-adjusted  $IC_{50}$  val-

ues, which may be too low for defining an adequate target level. Approximately 60% of patients in both arms were receiving ritonavir; since such patients were already receiving pharmacokinetically enhanced regimens, they may have stood little chance to benefit from therapeutic drug monitoring. Finally, there was a delay of 8 weeks from the start of treatment until a change in dosing or treatment based on therapeutic drug monitoring. Exposure of virus to suboptimal drug concentrations over this period could have resulted in emergence of resistance by the time treatment changes were made, preventing a beneficial effect on the longer-term virologic outcome. Additional data on the efficacy and benefits of therapeutic drug monitoring are needed.

In conclusion, the potential clinical role of therapeutic drug monitoring is under investigation, but remains a controversial issue. There are at present a number of settings in which therapeutic drug monitoring might be considered in patients receiving antiretroviral drugs, including:

- Confirmation of adequate drug concentrations in children
- Confirmation of adequate concentrations in patients with renal or hepatic dysfunction
- Evaluation of the effects of drug interactions and herbal remedies (eg, St. John's wort) on drug concentrations
- Evaluation of unexplained treatment failure
- Evaluation of exaggerated toxicity





Reasons for not performing therapeutic drug monitoring include the fact that the determination of optimal drug levels remains complicated, with even experts not being able to agree on correct target values. Further, there is considerable variability in intraindividual and interindividual pharmacokinetics of many antiretroviral drugs, as well as variability and lack of standardization of laboratory findings regarding both pharmacokinetics and drug inhibitory concentrations. In the clinical setting, reasons to not perform therapeutic drug monitoring include the suspicion that drug failure is more likely to be associated with nonadherence; if nonadherence is suspected, it may be the cause of reduced antiretroviral efficacy. Finally, there is little reason to monitor drug levels in patients doing well on their current regimen.

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