

## Review

# The Potential Role of Therapeutic Drug Monitoring in the Treatment of HIV Infection

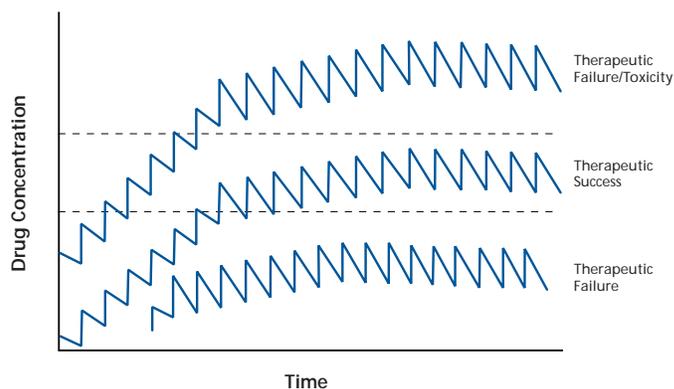
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**Abstract.** Therapeutic drug monitoring (TDM) is increasingly being used in clinical practice in order to improve the therapeutic outcome in HIV infection. The use of TDM requires certain pharmacologic, analytical, and clinical criteria in order to interpret the plasma concentrations appropriately. In this context, we have reviewed whether there are enough data to recommend the widespread use of TDM in the treatment of HIV infection. Nucleoside reverse transcriptase inhibitors are prodrugs that require intracellular metabolism for activity, so as a group they would not qualify for TDM in plasma. Although TDM potentially could be helpful in improving the efficacy and reducing the toxicity of protease inhibitors and nonnucleoside reverse transcriptase inhibitors, without clearly defined therapeutic ranges for many of these drugs and with few prospective TDM trials showing efficacy, plasma TDM has to be considered as an experimental tool in most clinical settings.

Therapeutic drug monitoring (TDM) is defined as a strategy by which the dosing regimen for a patient is guided by repeated measurements of plasma drug concentrations. If the concentration is not within a predefined target range, the dose is adjusted to bring this level within this target range (Figure 1). The 2 main reasons to undertake TDM in clinical situations are to avoid drug toxicity and to improve therapeutic efficacy. The history of TDM in clinical medicine is relatively brief, even though the concept that both efficacy and toxicity of a drug are dose- and concentration-dependent has been well established. Use of TDM in clinical medicine has been clearly linked to the development of assays that are accurate, sensitive, specific, and have a rapid turnaround time.

Although TDM is used in the treatment of several diseases, there is very little rigorous scientific evidence that its use has improved clinical outcome in patients.<sup>1</sup> The use of TDM in the prevention of drug toxicity has a stronger basis than the use of TDM for improved efficacy. This should not be surprising since therapeutic outcome is multifactorial and includes the importance of individual drug-taking behavior. For the treatment of HIV infection, TDM has another layer of complexity: incomplete viral suppression during therapy may result in HIV mutations so that drug susceptibility may become a moving target. This is quite unique compared with other diseases where TDM has been applied, in which the target concentration range remains the same throughout therapy.

The use of TDM in the pharmacotherapy of HIV infection is gaining momentum despite the fact that there are no clear-cut therapeutic ranges established for any of the antiretroviral drugs. HIV treatment requires the concomitant use of multiple drugs for durable viral suppression; however, TDM usually involves the monitoring of only a single drug concentration. The utility of TDM to improve therapeutic outcomes in HIV-infected patients has not been definitively demonstrated in large clinical trials, and therefore its use should be considered investigational. In this article we will review the criteria required for the use of TDM in clinical medicine and evaluate how antiretroviral drugs fare in this regard. In addition, we will review data from the few prospective clinical trials that have been published or presented that address the utility of TDM in the management of HIV infection. Unfortunately, there are no prospective studies that have attempted to measure the cost-effectiveness of TDM in the treatment of HIV infection.



**Figure 1.** The mechanism by which therapeutic concentrations for a drug can be established. The ordinate represents drug concentration and the abscissa represents a time factor on therapy. The bottom saw-toothed line shows concentrations where therapeutic failure results from suboptimal drug concentration. The middle line represents the optimal drug concentration for therapeutic success. The top line shows the concentrations that result in therapeutic failure secondary to toxicity from high drug concentrations.

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**Table 1.** Characteristics of Antiretroviral Drugs Applicable for Therapeutic Drug Monitoring

Criteria	Evaluation
<b>Analytical</b>	
Drug assay is accurate, specific, precise, requires small sample volume, yields rapid results, and is inexpensive	√
<b>Pharmacokinetic</b>	
Pharmacokinetic data are available	√
Significant interpatient pharmacokinetic variability exists	√
<b>Pharmacologic</b>	
Pharmacologic effect is related to drug concentration	√
Drug has a narrow therapeutic index	±
Drug has constant pharmacologic effect over extended period of time	±*
<b>Clinical</b>	
Clinical studies have documented the therapeutic and toxic ranges of the drug	±

√ indicates sufficient data are available for antiretroviral drugs to meet the specified criterion; ± indicates some data are available but the criterion has not been met. \*Depends on the extent of viral inhibition. Adapted from Spector et al, *Clin Pharmacol Ther*, 1988.

### Criteria for TDM Use in Clinical Medicine

The required criteria for the use of TDM in clinical medicine were described by Spector and colleagues in 1988.<sup>2</sup> These criteria are reviewed below in the context of antiretroviral drugs and characteristics that make drugs candidates for TDM (Table 1).

#### Analytical Criteria

*A drug assay is available with high specificity, small sample volume requirements, reasonable cost, and rapid turnaround time.*

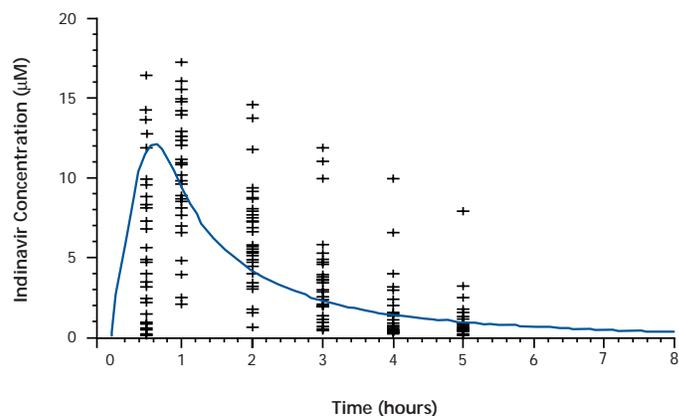
Very sensitive and specific assays are available for all the protease inhibitors, nonnucleoside reverse transcriptase inhibitors (NNRTIs), and nucleoside reverse transcriptase inhibitors (nRTIs) using high-performance liquid chromatography with ultraviolet (HPLC-UV) detection or liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS). However, nRTIs are more complex than protease inhibitors and NNRTIs since they circulate in the plasma as prodrugs and require intracellular phosphorylation to the active triphosphate metabolite. As a result, plasma concentrations of nRTIs may not always reflect activity in the intracellular compartment. A good example is didanosine, which has a very short plasma half-life but a long intracellular half-life and duration of action.<sup>3</sup> Since it has been

very difficult to measure accurately the intracellular concentrations of many nRTI triphosphates, nRTIs may not be good candidates for TDM and thus will not be included in the discussion of the other criteria for TDM. The analytical criteria required for application of TDM is met by the protease inhibitors and NNRTIs; the cost and turnaround time criteria will likely be met as more laboratories undertake the analysis of these drugs.

#### Pharmacokinetic Criteria

*There is significant interindividual variability in pharmacokinetics, resulting in large variability in achieved plasma concentrations. Adequate pharmacokinetic data concerning the drug are available.*

Although a fixed dose is administered to all adults taking protease inhibitors and NNRTIs, large variability in achieved plasma concentrations has been well documented for all the drugs in clinical use.<sup>4-7</sup> A number of pharmacokinetic studies have been conducted on currently available antiretroviral drugs as reviewed in a recent position paper on TDM.<sup>8</sup> All protease inhibitors have large intersubject variability in achieved plasma concentration following fixed-dose administration (Figure 2). This variability becomes a concern when the achieved trough concentration is below the concentration necessary for inhibition of viral replication, thereby creating the potential for the evolution of drug-resistant isolates. Administration of ritonavir with other protease inhibitors tends to reduce the pharmacokinetic variability of the protease inhibitors, but the intersubject variability still remains high.<sup>9</sup> Large interindividual variability is also present with achieved plasma concentrations of NNRTIs, yet it is unclear whether failure of NNRTI-based therapy is due to low plasma concentrations. Achieved plasma concentrations for nevirapine are orders of magnitude higher than what is required for viral inhibition in vitro.<sup>10</sup> However, quasi species with high-level drug resistance circulate as minority strains, and therefore adequate exposure to concomitant nRTIs is likely crucial in maintaining successful therapy with most of the NNRTIs.



**Figure 2.** The extreme variability of the pharmacokinetics of a protease inhibitor (indinavir) following standard dosing (800 mg q8h). Similar data showing large intersubject variability in pharmacokinetics are available for other protease inhibitors. Adapted with permission from Acosta et al, *Pharmacotherapy*, 1999.

There are many reasons behind pharmacokinetic variability of these lipophilic drugs. There is undoubtedly variability in drug solubilization and absorption from the intestinal tract. Multidrug-resistant proteins such as P-glycoprotein likely impede the bioavailability of protease inhibitors. In addition, the large variability of CYP3A expression in the small intestine and the liver can result in significant variability in the drug's bioavailability and systemic clearance. Based upon the large intersubject pharmacokinetic variability of protease inhibitors and NNRTIs and the sufficient data available on their pharmacokinetic profiles, both drug classes qualify for TDM.

### Pharmacologic Criteria

*Pharmacologic effect is proportional to the plasma drug concentration. A narrow range exists between the efficacious and toxic concentrations. A constant pharmacologic effect over an extended period of time exists.*

Higher plasma concentrations of protease inhibitors have resulted in a greater HIV-1 RNA response during initial dose-ranging studies as well as in clinical trials. This is not surprising since the basic tenet of pharmacology is that a concentration-response relationship exists with all clinically active drugs. Under certain circumstances, however, this relationship may not always hold true. One is the presence of active metabolites that can contribute to the overall therapeutic activity of the drug. Of the available protease inhibitors and NNRTIs, only nelfinavir is associated with a measurable active metabolite in the plasma.<sup>11</sup> The hydroxylated metabolite is designated as M-8 and is generated by nelfinavir's oxidation by CYP2C19.<sup>12</sup> M-8 and nelfinavir have equipotent in vitro activity against HIV. At this point, it is unclear to what extent the M-8 metabolite contributes to the overall antiretroviral activity after nelfinavir administration. It is likely that M-8 plasma binding is significantly less than nelfinavir plasma binding, so that the fraction of the drug that equilibrates intracellularly may be higher for M-8 than for nelfinavir. More research is required since in clinical use nelfinavir appears to be more effective than what would be predicted from its plasma concentration alone.

Protein binding is another factor influencing the concentration-response relationship for protease inhibitors because changes in overall binding of these drugs could affect the way total drug concentrations are interpreted. HIV replication occurs within cells, and protease inhibitors have to reach their intracellular target for activity. At equilibrium, the unbound concentration of a drug in plasma should be equivalent to the unbound concentration in the cell as long as there are no energy-dependent pumps that can transport drugs against a concentration gradient. The importance of the unbound concentration of a drug for activity was clearly demonstrated by the lack of clinical activity of the protease inhibitor SC-52151.<sup>13</sup> Because of its high degree of protein binding, the drug showed no activity despite achieving seemingly adequate plasma concentration based on in vitro anti-HIV activity.

Protease inhibitors are organic bases that are mostly bound in plasma to  $\alpha_1$ -acid glycoproteins (AAGs), which are acute-phase reactants whose concentrations increase under conditions of infection and acute inflammation.<sup>14</sup> The extent of protein binding of protease inhibitors is dependent upon the con-

centration of AAGs.<sup>15</sup> Higher concentrations of AAGs result in increased protein binding of protease inhibitors. Changes in protein binding for drugs like indinavir, which is only 60% plasma bound, will not greatly affect plasma-unbound concentrations and antiretroviral activity. In contrast, changes in protein binding for highly protein-bound drugs, such as nelfinavir and lopinavir, will significantly alter their activity at an equivalent plasma concentration. Thus when total plasma concentration of a highly protein-bound drug is interpreted, the same concentration with variable protein binding may not translate into equivalent antiretroviral activity. Nonetheless, there is some evidence that the pharmacologic effect of protease inhibitors is proportional to the plasma concentration in drug-naive subjects.<sup>16</sup>

The treatment of HIV infection requires multiple drugs for durable efficacy. For NNRTIs, the concentration-response relationship is less firmly established, but data with efavirenz increasingly point in that direction.<sup>7</sup> It is presently unclear if concomitant use of all the nRTIs will result in an equivalent antiretroviral efficacy at a specific protease inhibitor or NNRTI concentration. It is this high level of pharmacologic complexity in the treatment of HIV infection that makes the relationship between plasma concentration of protease inhibitors and antiretroviral response difficult to predict.

The therapeutic ranges for protease inhibitors and NNRTIs are difficult to evaluate because most drugs cannot be pushed to maximally tolerated doses. There are both absorption and tolerability limitations for these agents. It is likely that most drugs used in the treatment of HIV infection have a narrow range between the tolerated dose and the systemic concentration required for durable suppression. Gatti and colleagues clearly demonstrated that adverse effects of ritonavir are correlated to both peak and trough concentrations.<sup>17</sup> The tolerability of ritonavir is dose dependent and most patients do not tolerate the usual dose necessary for durable antiretroviral efficacy, 600 mg twice daily. Consequently, ritonavir is used mainly as a metabolic inhibitor of other protease inhibitors at a lower and better-tolerated dose.

For nelfinavir, for which most of the toxicity is gastrointestinal, there is no relationship between plasma concentration and the development of diarrhea.<sup>18</sup> Nephrotoxicity caused by indinavir has been related to a peak plasma concentration ( $C_{max}$ ) above 10  $\mu\text{g/mL}$ .<sup>19</sup> Since indinavir has a very short plasma half-life, a large amount of drug has to be administered to maintain adequate trough concentrations ( $C_{trough}$ ). As a result, the peak/trough ratio for indinavir is the highest among the protease inhibitors. The high  $C_{max}$  of indinavir can be manipulated by using lower indinavir doses with low-dose ritonavir to prolong the drug's plasma half-life.<sup>20</sup>

For NNRTIs, central nervous system (CNS) toxicity associated with efavirenz has been shown to be related to plasma concentration, and the concentration necessary for maximal activity is not far from the concentration that results in CNS toxicity.<sup>7</sup>

The presence or evolution of resistant viral strains will determine whether antiretroviral drugs exhibit a constant pharmacologic effect over an extended period of time. The HIV reverse transcriptase gene does not contain a "proofreading" mechanism, and as long as the virus is replicating, it can generate mutations that confer reduced susceptibility to antiretroviral drugs. If viral replication is contained, a constant pharmaco-

logic effect over an extended period of time does indeed occur for both the protease inhibitors and the NNRTIs. If mutated and phenotypically less susceptible viral strains evolve during therapy, the pharmacologic effect is not constant over even a short period of time. Higher concentrations of drugs may need to be achieved to control viral replication to the same extent as during initial therapy.

Based on these pharmacologic criteria, the applicability of TDM to antiretroviral drugs is variable. Since treatment of HIV infection requires the concomitant use of multiple drugs, monitoring only a single drug (eg, a protease inhibitor or NNRTI) may not be appropriate. Both the therapeutic efficacy and the toxicity of protease inhibitors and NNRTIs may demonstrate synergy, antagonism, or additive effects when combined with the various nRTIs or each other. The presence of baseline minority drug-resistant mutations and the evolution of drug resistance over time can make the concentration necessary for antiretroviral efficacy a moving target.

### Clinical Criteria

*Clinical studies exist that define the therapeutic and toxic ranges of the drug.*

A therapeutic range has not been formally defined for all drugs in clinical use for HIV, but concentration-response data are available for most of the protease inhibitors and NNRTIs. One problem is the uncertainty as to which pharmacokinetic parameter best defines the therapeutic and toxic exposures of the drugs. The  $C_{\text{trough}}$  is usually monitored to determine adequate drug exposure because it is the easiest to collect for both the patient and the investigator; however, this parameter requires an accurate recall of when the last dose of the drug was administered. Calculating an accurate area-under-the-curve value would require obtaining specimens over an extended period of time, which is unrealistic in a busy clinical setting. Logically,  $C_{\text{trough}}$  should define the lowest drug concentration during a dosage interval and thus define the minimum effective concentration of the drug, but this has not been prospectively validated for any of the antiretroviral drugs.

In terms of toxicity, the trough and the peak drug concentrations each may play an important role. For example,  $C_{\text{max}}$  may best approximate the risk of indinavir-induced nephrotoxicity,<sup>19</sup> but other toxicities such as skin and nail abnormalities may be related to total drug exposure. Marzolini and colleagues attempted to define the therapeutic range of efavirenz by retrospectively correlating CNS toxicity with plasma concentrations in a small group of subjects, some of whom were experiencing virologic failure.<sup>7</sup> Although this may be one way to define the therapeutic ranges for drugs, prospective studies that validate these drug concentrations with observations of efficacy and toxicity would certainly strengthen the argument for TDM.

In drug-naïve subjects, the  $C_{\text{trough}}$  necessary for continued viral suppression has been defined best for indinavir. This concentration is approximately 100 ng/mL, which is close to the protein-binding-corrected 95% inhibitory concentration for indinavir in vitro.<sup>16</sup> However, the determination of the  $C_{\text{trough}}$  necessary for durable virologic suppression is made in the presence of concomitant nRTIs, and whether all of the nRTIs interact with the protease inhibitors at the same potency in vivo has not been

studied. Abacavir, for example, which is a much more potent antiretroviral drug than stavudine, may quantitatively contribute to successful therapy more than stavudine when used concomitantly with protease inhibitors.<sup>21,22</sup>

### Prospective Clinical Trials

There are only a few prospective studies that have examined the utility of TDM in the treatment of HIV. ATHENA was a prospective trial of TDM in which analyses of a subgroup of patients on indinavir or nelfinavir were performed.<sup>23</sup> Ninety-two treatment-naïve patients were randomized to receive nelfinavir 1250 mg twice daily using TDM or no TDM. A concentration ratio (CR) was used to assess drug exposure and make dosing modifications in the TDM group. A measured drug level (drawn at any time following an unobserved dose) was compared with a population average concentration-time curve. A ratio of 1 meant the patient's concentration was the same as the population average on that occasion. If the first nelfinavir CR was less than 0.9, taking the drug with food was discussed with the patient. If the subsequent CR remained less than 0.9, the dose was increased to 1500 mg twice daily, and low-dose ritonavir was added if the third CR was low. The average turnaround time for the assay results was 4 weeks.

By intent-to-treat (ITT) analysis, the proportions of patients achieving plasma HIV-1 RNA levels below 500 copies/mL at 1 year were 81% and 59% in the TDM and no-TDM groups, respectively ( $P=.03$ ). The authors suggested that these results reflected differences in drug efficacy because the main reason for drug discontinuation in the no-TDM group was virologic failure, which was more frequent for the no-TDM group.

The ATHENA study also examined the effect of TDM in subjects receiving indinavir 800 mg 3 times a day, indinavir 800 mg with 100 mg ritonavir twice daily, or indinavir plus ritonavir at 400 mg each twice daily. The acceptable CR for indinavir was defined as 0.75 to 2.0. This analysis showed more favorable outcomes in the group randomized to TDM. By ITT analysis, 75% and 48% of subjects had plasma HIV-1 RNA levels below 500 copies/mL in the TDM and no-TDM arms, respectively, at 1 year. This difference was secondary to toxicity, since there were very few virologic failures and far fewer subjects in the TDM arm dropped out of the study for toxicity reasons than those in the no-TDM arm. These data suggest that TDM may be potentially useful in the management of antiretroviral therapy for both efficacy and toxicity reasons. Although these substudies of the ATHENA trial had positive results, concerns remain regarding the statistical power of the study to detect differences between groups and whether clinicians truly followed dose change recommendations.

PharmAdapt was a prospective study comparing the use of TDM versus no TDM in treatment-experienced patients in whom therapy failed.<sup>24,25</sup> A total of 257 subjects enrolled in this study, but the presented data were limited to 180 subjects receiving protease inhibitor-containing regimens. Ninety-six subjects were in the control group and 84 subjects were in the TDM group. All subjects had genotypic resistance testing prior to randomization, and drug therapy was determined on the basis of these results. The TDM group had a dose modification at week 8 based on week 4 trough concentrations. The targeted protease

inhibitor exposure was a trough concentration above the protein-binding-corrected median inhibitory concentration ( $IC_{50}$ ) of wild-type HIV described in the literature. At week 8, 6% of the control group had a physician-determined protease inhibitor dose modification. Physician- and protocol-driven dose modifications occurred in 17% of subjects in the TDM group. At week 12, the change in plasma HIV-1 RNA level was equivalent in both groups ( $-2.61 \log_{10}$  in the control group;  $-2.32 \log_{10}$  in the TDM group). Also at week 12, plasma HIV-1 RNA levels below 200 copies/mL were observed in 52% of the control group and 45% of the TDM group. A 32-week analysis reported virologic effects in the 2 groups similar to those at week 12.

This TDM study was the first to report negative results; however, concerns regarding the study design deserve comment. It is unclear how the protein-binding-corrected  $IC_{50}$  was chosen as the appropriate target concentration for protease inhibitors. In addition, it is likely that wild-type  $IC_{50}$  concentrations were too low for an adequate antiviral response in the majority of drug-experienced subjects. Furthermore, dosage adjustment at week 8 may have been too late to prevent evolution of the virus in a group of subjects in whom protease inhibitor-based regimens were failing. Finally, a power analysis was not performed. If 17% of subjects required dose modification in the TDM group versus 6% in the control group, a sample size greater than 180 may have been necessary to demonstrate virologic differences across treatment approaches.

A prospective, randomized clinical trial evaluating concentration-controlled versus fixed-dose therapy with zidovudine/lamivudine/indinavir in 40 treatment-naive patients has been reported by Fletcher and colleagues.<sup>26</sup> Subjects in the fixed-dose arm received standard zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, and indinavir 800 mg every 8 hours. Subjects randomized to the concentration-controlled arm received doses to maintain plasma concentrations of at least 0.17, 0.4, and 0.13 mg/L for zidovudine, lamivudine, and indinavir, respectively. Treatment duration was 52 weeks, and adherence was measured using the ratio of medication taken (derived from pill counts) to that prescribed. Intensive pharmacokinetic analyses were made at week 2, and secondary pharmacokinetic measurements were made at week 28. Dose changes in the concentration-controlled arm were implemented at week 4 based on the pharmacokinetic data collected at week 2, and a Bayesian-estimation feedback algorithm was employed using subsequent single concentration-time points for further dosage refinement. Sample-size calculation was based on variability in drug exposure, toxicity, and differences in plasma HIV-1 RNA level at the 5% significance level with 80% power. Seven subjects terminated the study early and were not included in the pharmacokinetic or virologic analyses. Zidovudine, lamivudine, and indinavir doses were altered in 44%, 31%, and 81% of the concentration-controlled recipients, respectively.

At 52 weeks, in an ITT analysis, 15 of 16 subjects (94%) in the concentration-controlled arm and 9 of 17 subjects (53%) in the fixed-dose arm achieved plasma HIV-1 RNA levels below 50 copies/mL ( $P=.017$ ). The concentration-controlled group reached undetectable plasma HIV-1 RNA levels more rapidly than the fixed-dose group: 108 days versus 225 days, respectively ( $P=.01$ ). No significant differences were found between groups in terms of occurrence of common adverse events,

including anemia, neutropenia, and nephrolithiasis. Average adherence rates exceeded 90% for all 3 drugs in both arms and were not statistically different between the treatment groups.

This is the longest prospective TDM trial reported to date, and the first one to apply TDM to all drugs in a regimen of highly active antiretroviral therapy (HAART). The study investigators concluded that a single-dose approach to treat all patients with HIV infection may not be optimal. Although this latter study is the most rigorously conducted of the three, the use of indinavir alone as the protease inhibitor in a HAART regimen is now fairly unusual. Many physicians now routinely prescribe indinavir with low-dose ritonavir, which results in higher plasma indinavir concentrations than indinavir alone.

## Conclusions

Where are we in terms of using TDM for managing antiretroviral drug use in clinical HIV medicine? Widespread use of TDM is not appropriate at this time. Obtaining random plasma concentrations of drugs with very short plasma half-lives makes interpretation of these data difficult. Using TDM to assess adherence to therapy is also not an appropriate use of plasma concentrations for drugs with short half-lives.

It is critical to determine why multidrug therapy for HIV infection fails. If in most cases failure is secondary to poor adherence, then TDM is not the correct way to improve outcome. Data from Fischl and colleagues, which compared the results of using directly observed therapy (DOT) with self-administered therapy in antiretroviral drug-naive subjects, indicate that a major hurdle to therapeutic success in these patients is adherence to drug administration.<sup>27</sup> In that study, results at week 88 showed that all subjects in the DOT group had plasma HIV-1 RNA levels below 400 copies/mL; in the self-administered therapy group, approximately 80% had levels below 400 copies/mL. The percent achieving plasma HIV-1 RNA levels below 50 copies/mL in the 2 groups was 93% and 60%, respectively.

If the intent of TDM is to identify a small percentage of patients who are rapid metabolizers of drugs, performing TDM early in therapy after reaching a presumed steady-state concentration may be appropriate. TDM may also be an appropriate way to reduce drug toxicity if data from retrospective clinical studies indicate a concentration of the drug above which many patients develop toxicity. However, a prospective study would be important to confirm that this toxicity can be circumvented using TDM. Cost-effectiveness analysis should also be a component of all clinical trials utilizing TDM.

TDM also may be appropriate in cases where another drug needs to be added to a successful therapeutic regimen in which a drug-drug interaction is possible. Obtaining a plasma concentration of the current drug prior to the addition of the new drug would define the current drug's therapeutic concentration for that person, which would then be the target concentration after the addition of the new drug. For example, if phenytoin, an inducer of drug-metabolizing enzymes, needs to be added to a successful protease inhibitor-based regimen, the protease inhibitor concentrations will likely be much lower following the addition of phenytoin, and checking a drug level may be useful to ensure it is not below the average level observed in patients.

In the treatment of drug-experienced subjects who have drug-resistant virus, determining a protein-corrected  $IC_{50}$  may be useful. Applying TDM to then achieve a concentration several-fold above that  $IC_{50}$  would seem reasonable. Evaluation of the inhibitory quotient (IQ), in which the phenotypic sensitivity of the virus to the drug and the plasma concentration of the drug determine the IQ, is being studied in clinical trials. Well-designed and adequately powered prospective studies need to be performed before IQ can be generally recommended for clinical practice.

The important message about TDM is that it may ultimately prove useful, but at this time there are not enough data to recommend its use outside of very specific circumstances. TDM should currently be viewed as an investigational tool to explore means of improving therapeutic outcome and reducing toxicities in the treatment of HIV infection.

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