Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Exposure-Response Relationship and Therapeutic Drug Monitoring (TDM) for Antiretroviral Agents (Last updated January 10, 2011; last reviewed January 10, 2011)

Panel's Recommendations
• Therapeutic drug monitoring (TDM) for antiretroviral (ARV) agents is not recommended for routine use in the management of the HIV-infected adult **(CIII)**. • TDM may be considered in selected clinical scenarios, as discussed in the text below.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Knowledge of the relationship between systemic exposure (or concentration) and drug responses (beneficial and/or adverse) is key in selecting the dose of a drug, in understanding the variability in the response of patients to a drug, and in designing strategies to optimize response and tolerability.

TDM is a strategy applied to certain antiarrhythmics, anticonvulsants, antineoplastics, and antibiotics that utilizes measured drug concentrations to design dosing regimens to improve the likelihood of the desired therapeutic and safety outcomes. The key characteristic of a drug that is a candidate for TDM is knowledge of the exposure-response relationship and a therapeutic range of concentrations. The therapeutic range is a range of concentrations established through clinical investigations that are associated with a greater likelihood of achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions.

Several ARV agents meet most of the characteristics of agents that can be considered candidates for a TDM strategy.[1] The rationale for TDM in managing antiretroviral therapy (ART) derives from the following:

- data showing that considerable interpatient variability in drug concentrations exists among patients who take the same dose;
- data indicating that relationships exist between the concentration of drug in the body and anti-HIV effect and, in some cases, toxicities; and
- data from small prospective studies demonstrating that TDM improved virologic response and/or decreased the incidence of concentration-related drug toxicities.[2-3]

TDM for ARV agents, however, is not recommended for routine use in the management of the HIV-infected adult (CIII).

Multiple factors limit the routine use of TDM in HIV-infected adults.[4-5] These factors include:

- lack of large prospective studies demonstrating that TDM improves clinical and virologic outcomes. (This is the most important limiting factor for the implementation of TDM at present.);
- lack of established therapeutic range of concentrations for all ARV drugs that is associated with achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions;
- intrapatient variability in ARV drug concentrations;
- lack of widespread availability of clinical laboratories that perform quantitation of ARV concentrations under rigorous quality assurance/quality control standards; and
- shortage of experts to assist with interpretation of ARV concentration data and application of such data to revise patients' dosing regimens.

Exposure-Response Relationships and TDM with Different ARV Classes

Protease Inhibitors (PIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), and Integrase Inhibitors. Relationships between the systemic exposure to PIs and NNRTIs and treatment response have been reviewed in various publications.[4-7] Although there are limitations and unanswered questions, the consensus among clinical pharmacologists from the United States and Europe is that the data provide a framework for the potential implementation of TDM for PIs and NNRTIs. However, information on relationships between concentrations and drug-associated toxicities are sparse. Clinicians who use TDM as a strategy to manage either ARV response or toxicities should consult the most current data on the proposed therapeutic concentration range. Exposure-response data for darunavir (DRV), etravirine (ETR), and raltegravir (RAL) are accumulating but are not sufficient to recommend minimum trough concentrations. The median trough concentrations for these agents in HIV-infected persons receiving the recommended dose are included in Table 9b.

CCR5 Antagonists. Trough maraviroc (MVC) concentrations have been shown to be an important predictor of virologic success in studies conducted in ART-experienced persons.[8-9] Clinical experience in the use of TDM for MVC, however, is very limited. Nonetheless, as with PIs and NNRTIs, the exposure-response data provide a framework for TDM, and that information is presented in these guidelines (Table 9b).

Nucleoside Reverse Transcriptase Inhibitors (NRTIs). Relationships between plasma concentrations of NRTIs and their intracellular pharmacologically active moieties have not yet been established. Therefore, monitoring of plasma or intracellular NRTI concentrations for an individual patient largely remains a research tool. Measurement of plasma concentrations, however, is routinely used for studies of drug-drug interactions.

Scenarios for Use of TDM. Multiple scenarios exist in which both ARV concentration data and expert opinion may be useful in patient management. Consultation with a clinical pharmacologist or a clinical pharmacist with HIV expertise may be advisable in these cases. These scenarios include the following:

- Suspect clinically significant drug-drug or drug-food interactions that may result in reduced efficacy or increased dose-related toxicities;
- Changes in pathophysiologic states that may impair gastrointestinal, hepatic, or renal function, thereby potentially altering drug absorption, distribution, metabolism, or elimination;
- Pregnant women who may be at risk of virologic failure as a result of changes in their pharmacokinetic parameters during the later stage of pregnancy, which may result in plasma concentrations lower than those achieved in the earlier stages of pregnancy and in the nonpregnant patient;
- Heavily pretreated patients experiencing virologic failure and who may have viral isolates with reduced susceptibility to ARVs;
- Use of alternative dosing regimens and ARV combinations for which safety and efficacy have not been established in clinical trials;
- Concentration-dependent, drug-associated toxicities; and
- Lack of expected virologic response in medication-adherent persons.

TDM

- **For patients who have drug-susceptible virus.** Table 9a includes a synthesis of recommendations[2-7] for minimum target trough PI and NNRTI concentrations in persons with drug-susceptible virus.
- **For ART-experienced patients with virologic failure** (see Table 9b). Fewer data are available to formulate suggestions for minimum target trough concentrations in ART-experienced patients who have viral isolates with reduced susceptibility to ARV agents. Concentration recommendations for tipranavir

(TPV) and MVC were derived only from studies in ART-experienced persons. It is likely that use of PIs and NNRTIs in the setting of reduced viral susceptibility may require higher trough concentrations than those needed for wild-type virus. The inhibitory quotient (IQ), which is the ratio of ARV drug concentration to a measure of susceptibility (genotype or phenotype) of the patient's strain of HIV to that drug, may additionally improve prediction of virologic response—as has been shown, for example, with DRV in ART-experienced persons.[10-11] Exposure-response data for DRV, ETR, and RAL are accumulating but are not sufficient to recommend minimum trough concentrations. The median trough concentrations for these agents in HIV-infected persons receiving the recommended dose are included in Table 9b.

Using Drug Concentrations to Guide Therapy. There are several challenges and considerations for implementation of TDM in the clinical setting. Use of TDM to monitor ARV concentrations in a patient requires multiple steps:

- quantification of the concentration of the drug, usually in plasma or serum;
- determination of the patient's pharmacokinetic characteristics;
- integration of information on patient adherence;
- interpretation of the concentrations; and
- adjustment of the drug dose to achieve concentrations within the therapeutic range, if necessary.

Guidelines for the collection of blood samples and other practical suggestions can be found in a position paper by the Adult AIDS Clinical Trials Group Pharmacology Committee.[4]

A final caveat to the use of measured drug concentrations in patient management is a general one—drug concentration information cannot be used alone; it must be integrated with other clinical information. In addition, as knowledge of associations between ARV concentrations and virologic response continues to accumulate, clinicians who employ a TDM strategy for patient management should consult the most current literature.

Table 9a. Trough Concentrations of Antiretroviral Drugs for Patients Who Have Drug-Susceptible Virus

Drug	Concentration (ng/mL)
Suggested minimum target trough concentrations in patients with HIV-1 susceptible to the ARV drugs[2-9]	
Fosamprenavir (FPV)	400 (measured as amprenavir concentration)
Atazanavir (ATV)	150
Indinavir (IDV)	100
Lopinavir (LPV)	1000
Nelfinavir[a] (NFV)	800
Saquinavir (SQV)	100–250
Efavirenz (EFV)	1000
Nevirapine (NVP)	3000

[a] Measurable active (M8) metabolite

Table 9b. Trough Concentrations of Antiretroviral Drugs for Treatment-Experienced Patients with Virologic Failure

Drug	Concentration (ng/mL)
Suggested minimum target trough concentrations for ART-experienced patients who have resistant HIV-1 strains	
Maraviroc (MVC)	>50
Tipranavir (TPV)	20,500
Median (Range) Trough Concentrations from Clinical Trials[12-14]	
Darunavir (DRV) (600 mg twice daily)	3300 (1255–7368)
Etravirine (ETR)	275 (81–2980)
Raltegravir (RAL)	72 (29–118)

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