



## **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 April 8, 2015; last reviewed April 8, 2015)

### Panel's Recommendations

- Therapeutic drug monitoring (TDM) for antiretroviral agents is not recommended for routine use in the management of patients with HIV (BII).
- 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 about the relationship between a drug's systemic exposure (or concentration) and responses (beneficial and/or adverse) is key in selecting the dose of a drug, in understanding why patients may respond differently to the same drug and dose, and in designing strategies to optimize drug response and tolerability.

Therapeutic drug monitoring (TDM) is a strategy used to guide dosing of certain antiarrhythmics, anticonvulsants, antineoplastics, and antimicrobial agents by using measured drug concentrations to improve the likelihood of the desired therapeutic and safety outcomes. Drugs suitable for TDM are characterized by a known 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 antiretroviral (ARV) agents meet most of the characteristics of agents suitable for a TDM strategy.<sup>1</sup> Specifically, some ARVs have considerable interpatient variability in drug concentrations. Other ARVs have known drug concentrations associated with efficacy and/or toxicity. In the case of other drugs, data from small prospective studies have demonstrated that TDM improved virologic response and/or decreased the incidence of concentration-related drug toxicities.<sup>2,3</sup>

**TDM for ARV agents, however, is not recommended for routine use in the management of adults and adolescents with HIV (BII).** This recommendation is based on multiple factors that limit the routine use of TDM in patients with HIV. These limiting factors include lack of prospective studies that demonstrate routine use of TDM improves clinical outcomes, uncertain therapeutic thresholds for most ARV agents, great intra- and inter-patient variability in drug concentrations achieved, and a lack of commercial laboratories to perform real time quantitation of ARV concentrations.<sup>2-5</sup>

### ***Scenarios for Consideration of Therapeutic Drug Monitoring***

Although routine use of TDM is not recommended, in some scenarios, ARV concentration data may be useful in patient management. In these cases, assistance from a clinical pharmacologist or a clinical pharmacist to interpret the concentration data may be advisable. These scenarios include the following:

- Suspicion of 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;
- Among pregnant women who have risk factors for virologic failure (e.g., those not achieving viral suppression during an earlier stage of pregnancy), physiologic changes may result in reduced drug exposure during the later stages of pregnancy and thus further increase the risk of virologic failure;
- 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
- Failure to achieve expected virologic response in medication-adherent patients.

### ***Resources for Therapeutic Drug Monitoring Target Concentrations***

Most TDM-proposed target concentrations for ARVs focus on a minimum concentration ( $C_{\min}$ ) (i.e., the plasma concentration at the end of a dosing interval before the next ARV dose). A summary of population average ARV  $C_{\min}$  can be found in a review on the role of ARV-related TDM.<sup>2</sup> Population average  $C_{\min}$  for newer ARVs can be found in the Food and Drug Administration-approved product labels.

Guidelines for the collection of blood samples and other practical suggestions related to TDM can be found in a position paper by the Adult AIDS Clinical Trials Group Pharmacology Committee.<sup>4</sup>

### ***Challenges and Considerations in 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 the following:

- 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 drug concentrations; and
- Adjustment of the drug dose to achieve concentrations within the therapeutic range, if necessary.

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, including the patient's ARV history and adherence before the TDM result. In addition, as knowledge of associations between ARV concentrations and virologic response evolves, clinicians who use a TDM strategy for patient management should evaluate the most up-to-date information regarding the exposure-response relationship of the tested ARV agent.

## **References**

1. Spector R, Park GD, Johnson GF, Vesell ES. Therapeutic drug monitoring. *Clin Pharmacol Ther.* 1988;43(4):345-353. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=3281773](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3281773).
2. Pretorius E, Klinker H, Rosenkranz B. The role of therapeutic drug monitoring in the management of patients with human immunodeficiency virus infection. *Ther Drug Monit.* 2011;33(3):265-274. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21566505>.
3. Kredo T, Van der Walt JS, Siegfried N, Cohen K. Therapeutic drug monitoring of antiretrovirals for people with HIV. *Cochrane Database Syst Rev.* 2009(3):CD007268. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19588422>.
4. Acosta EP, Gerber JG. Position paper on therapeutic drug monitoring of antiretroviral agents. *AIDS Res Hum Retroviruses.* 2002;18(12):825-834. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=12201904](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12201904).
5. van Luin M, Kuks PF, Burger DM. Use of therapeutic drug monitoring in HIV disease. *Curr Opin HIV AIDS.* 2008;3(3):266-271. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=19372977](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19372977).