Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Role of Therapeutic Drug Monitoring in Management of Treatment Failure (Last updated August 11, 2011; last reviewed November 1, 2012)

Therapeutic drug monitoring (TDM) is use of plasma drug concentration measurements as part of a strategy to optimize drug dosing to minimize toxicity and maximize treatment benefit. TDM can be considered for use in combination antiretroviral therapy because:[1, 2]

- Interpatient variability in antiretroviral (ARV) exposure (i.e., plasma drug concentrations) using standard recommended doses is high;
- Low drug exposure can lead to suboptimal virologic response to therapy; and
- High plasma concentrations can be associated with increased risk of drug toxicity.

Developmental pharmacokinetic differences contribute to greater variability and a greater frequency of suboptimal ARV exposure in pediatric patients than in adults.[3] Pediatric dosing is designed to mimic adult exposure and rarely reflects the maximum tolerated ARV drug dose. Even when using dose recommendations from published pediatric guidelines, children often receive inadequate ARV doses.[4]

There are two main situations in which TDM may be useful in a child who is failing therapy. First, TDM can be used to rule out subtherapeutic drug levels as a cause of failure. Such inadequate drug levels could result from malabsorption, drug interactions, poor adherence, or increased drug metabolism or clearance. Second, drug levels can be used to optimize drug dosage when changing to a new regimen in a patient whose virus has reduced susceptibility to that drug.

For TDM to be useful, the relationship between ARV drug concentrations and anti-HIV effects must be clearly defined.[5-7] This association is strongest with protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTIs),[8] but maintaining adequate nucleoside reverse transcriptase inhibitor (NRTI) serum concentrations also has been shown to be important for maximal anti-HIV activity.[9] The exposure-toxicity response relationship is less well defined for NRTI drugs but has been determined for some agents.[7] Concentration-response relationships have been established with minimum plasma concentrations (C_{min} or C_{trough}) or area under the curve (AUC), but the optimal measure is not defined for all ARV drugs.[10]

Table 21 presents recommendations for the minimum target trough concentrations of PIs and NNRTIs in patients without evidence of resistance to those drugs. In ARV-experienced patients, the choice of minimum target trough concentration should be based on results of resistance testing.[11-13] Although it is intrinsically difficult to demonstrate benefit of TDM using double-blind studies, limited data suggest targeted concentrations can be achieved with TDM, clinical responses can be improved with increased or modified doses, and TDM information can be helpful in decision making.[8, 14-18] Clinicians should consult with a pediatric HIV specialist or pharmacologist in making these decisions.

TDM is not recommended for routine use but may be considered potentially useful for patients:

- In whom clinical response is different from that expected;
- Who are treatment experienced and infected with virus with reduced drug susceptibility, where a comparison of the drug susceptibility of the virus and the achieved drug concentrations may be useful;
- Who may experience potential difficulties with drug administration related to suboptimal dietary intake or malabsorption, incorrect dosing or caregiver measuring errors, or concerns surrounding adherence; and
- Who experience drug or food interactions, including interactions resulting from alteration of drug formulations by crushing medications or mixing them with various foods and liquids.

Current limitations for pediatric ARV TDM include:

- Prolonged time for laboratory processing in the face of potentially diminishing benefit the longer a patient is on inadequate therapy;
- Difficulties in coordinating sample collections at appropriate times, which make determination of true C_{min} or AUC difficult;
- High intrapatient variability from single drug concentration measurements may complicate interpretation of results;[19, 20]
- Single trough measurements within the target range, which do not guarantee consistent adequacy of drug exposure or therapeutic success;
- Inadequate information on safety and effectiveness of dose adjustment strategies in children and adolescents;
- Limited availability of certified laboratories capable of assaying drug concentrations; and
- Lack of third-party reimbursement of costs associated with TDM.

Table 21. Suggested Minimum Target Trough Concentrations[a]

Drug	Concentration (ng/mL)
Atazanavir	150
Fosamprenavir	400 (measured as amprenavir concentration)
Indinavir	100
Lopinavir	1,000
Nelfinavir (measurable active [M8] metabolite)	800
Saquinavir	100–250
Efavirenz	1,000
Nevirapine	3,000
Recommendations applicable only to treatment-experienced persons who have resistant HIV-1 strains	
Maraviroc	>50
Tipranavir	20,500

[a] Reprinted from: *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Department of Health and Human Services. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.

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