# Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection



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# Role of Therapeutic Drug Monitoring in Management of Pediatric HIV Infection (Last updated April 27, 2017; last reviewed April 27, 2017)

| Panel's Recommendations |
|---|
| • Routine evaluation of plasma concentrations of antiretroviral (ARV) drugs is not generally recommended in the management of children with HIV infection **(BII)**<br>• Targeted therapeutic drug monitoring of ARV drugs in children can be considered in the following scenarios **(BII)**:<br>  • Use of ARV drugs with limited pharmacokinetic data and/or therapeutic experience in children;<br>  • Use of patient pharmacogenetic profile for the selection of the dose of certain ARV drugs (e.g. efavirenz);<br>  • Significant drug-drug and food-drug interactions;<br>  • Suboptimal treatment response (e.g., lack of virologic suppression) in medication-adherent patients;<br>  • Suspected suboptimal absorption, distribution, metabolism, or elimination of the drug; or<br>  • Suspected concentration-dependent drug-associated toxicity. |
| ***Rating of Recommendations:*** *A = Strong; B = Moderate; C = Optional*<br>***Rating of Evidence:*** *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*<br>† *Studies that include children or children/adolescents but not studies limited to postpubertal adolescents* |

The goal of therapeutic drug monitoring (TDM) of antiretroviral (ARV) drugs is to optimize treatment responses and tolerability, and to minimize drug-associated toxicity. TDM may be useful in clinical management with drugs that have a known exposure-response relationship and a relatively narrow therapeutic window of desirable concentrations. The therapeutic window is a range of concentrations that are associated with the greatest likelihood of achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions in clinical investigations. While many ARV drugs (e.g., most protease inhibitors, first-generation non-nucleoside reverse transcriptase inhibitors, the CCR5 receptor antagonist maraviroc) have target plasma trough concentrations associated with viral efficacy, only a few ARV drugs have drug levels associated with toxicity (e.g., nevirapine and efavirenz). Most TDM targets have been established in adult studies, but several drugs (e.g., lopinavir, nelfinavir, efavirenz, nevirapine) have had target concentrations validated in pediatric studies. The suggested efficacy plasma trough concentrations are generally applicable when resistance testing demonstrates susceptibility of the patient's virus to the particular ARV drug. Table 17 includes data on the efficacy plasma trough concentrations derived from adult clinical trials of the ARV drugs. Historically, most TDM target concentrations for ARV drugs focused on reaching a trough ($C_{trough}$) or minimum plasma concentration ($C_{min}$).[1] Population average $C_{min}$ for all ARV drugs (including newer ARV drugs) can be found in the Food and Drug Administration-approved product labels.

**Table 17. Target Trough Concentrations of Antiretroviral Drugs Relevant to Pediatric Populations[a]**

| Drug | Plasma Trough Concentration (ng/mL) ± Standard Deviation |
|---|---|
| Atazanavir | 2,000±1,000 |
| Darunavir | 2,200±1,100 |
| Fosamprenavir | 2,100 |
| Lopinavir | 5,500±4,000 |
| Nelfinavir | 700±400 |
| Efavirenz | 1,700±1,000 |
| Nevirapine | 4,500±1,900 |
| Etravirine | 300 |
| Tipranavir | 20,000–45,000 |
| Raltegravir | 65 |

[a] Adapted from: 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.

Several adult and pediatric studies have suggested that TDM can have some utility in assessing adherence, guiding dosing, and predicting efficacy of ARV drugs.[1-13] Despite this evidence, the routine use of TDM in adult and pediatric patients is not recommended for the following reasons: lack of prospective studies that demonstrate improved clinical outcomes, uncertain target ranges for most ARV drugs, high intrapatient and interpatient variability in drug concentrations, and a lack of commercial laboratories that provide real-time quantitation of ARV plasma concentrations.

There are special considerations with dosing of ARV drugs in children living with HIV compared to adults, including dependence on chronologic age and/or body parameters (e.g., height, weight). Ongoing growth requires continuous reassessment of dosing of ARV drugs in order to avoid low drug exposure and development of viral resistance and virologic failure. Developmental differences in drug absorption, distribution, metabolism, and elimination contribute to high variability and a greater frequency of suboptimal exposure to multiple therapeutic agents in children (particularly very young children) compared to adults.[14] Suboptimal exposure to selected ARV drugs has been demonstrated in pediatric patients, especially in young children; therefore TDM may be helpful in the management of pediatric antiretroviral therapy.[7,15-18]

TDM is also useful in children when pharmacogenetics considerations are important in selection of drug dosing. For example, the known effect of the metabolic enzyme CYP2B6 G516T polymorphism on the pharmacokinetics (PK) of efavirenz appears to be most pronounced in younger children undergoing maturation of CYP450 enzymatic system during the first 3 years of life, compared to older children and adults.[18] The significant effect of this polymorphism has prompted dosing guidelines to be based on the patient CYP2B6 G516T genotype of children aged <3 years, along with subsequent confirmation of the efavirenz exposure through TDM (see efavirenz).

Pediatric ARV drug recommendations are often based on extrapolation of efficacy results from large clinical trials in adults, and dosing recommendations for ARV drugs at the time of pediatric drug approval are frequently derived from a limited number of patients and PK modeling, and may be revised as newer PK data become available.[7] While the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV does not recommend routine TDM for pediatric antiretroviral therapy management, TDM can be considered for certain ARV agents when the approved pediatric formulation and/or dosing are based on limited PK and efficacy data in small populations (see specific drug information sections) or for certain clinical scenarios outlined in the text box above to ensure adequate drug concentrations and/or to decrease toxicity.

## *Practical Considerations*

The accurate interpretation of TDM requires evaluation and documentation of the following:

- The dose and formulation
- Concomitant medications
- Food intake with the dose
- Timing of the dose relative to blood sample collection
- Adherence and resistance information

Additional practical suggestions on TDM of ARV drugs can be found in a position paper by the Adult AIDS Clinical Trials Group Pharmacology Committee[19] and pediatric TDM manuscripts.[6,20] Most importantly, consultation with an expert in pediatric HIV pharmacology is strongly recommended to obtain guidance on when to obtain samples for TDM, how to interpret the PK data, and how to evaluate the need for dose adjustment and repeat PK evaluation and follow up.

## References


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