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Review

Pharmacokinetic targets of antiretroviral therapy in children and adolescents

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Abstract

Large populations of HIV-infected and exposed infants, children and adolescents are increasingly exposed to antiretroviral therapy throughout dramatic changes of the body composition and maturation process in utero, perinatally and during the later growth and development throughout childhood and puberty. The majority of HIV-infected children live in the resource-limited setting where the presence of other significant co-morbidities such as malnutrition, tuberculosis and malaria complicates the selection of the most effective, safe and least toxic combination of antiretroviral drug therapy. This review focuses on the role of the pharmacokinetic factors including clinically important drug-drug interactions on the therapeutic targets of antiretroviral therapy throughout childhood and adolescence.

Keywords

HIV/AIDS, Pediatrics, Pharmacokinetics, Pharmacodynamics, TDM.

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Introduction

HIV infection is estimated to affect 3.4 million children under the age of 15 years worldwide and, therefore, represents the most significant modern lifelong disease of pediatric medicine [1]. Although unable to cure the HIV infection, currently available antiretroviral therapy (ART) has significantly decreased HIV-associated morbidity and mortality, and improved survival and quality of life in hundreds of thousands of pediatric patients worldwide [2-4].

Significant progress has been made in the development of pediatric antiretroviral (ARV) drugs, their dosing and formulations. Just within the last 24 months in the United States seven pediatric ARV preparations (fosamprenavir [FPV], raltegravir [RAL], tenofovir disoproxil fumarate [TDF], etravirine [ETR], efavirenz [EFV], darunavir [DRV] and dolutegravir [DTG]) have been approved either for the first time in pediatric patients or for use in younger children, and ten generic pediatric preparations have been approved by the United States Food and Drug Administration (FDA) under the President's Emergency Plan for AIDS Relief (PEPFAR) for the use in resource limited settings [5]. As a result of these efforts, 20 of 24 unique ARV medications from all five therapeutic classes are now marketed as therapy for HIV infection in children under 16 years of age [6].

The main goals of ART in light of the current absence of cure are to achieve and sustain the maximal degrees of virologic suppression and immunologic recovery. All currently available ARV drugs either block HIV replication within infected human cells or prevent viral entry into the cells. Therefore, the efficacy of ART in the management of HIV infection in children and adolescents is measured through virologic suppression below detectable threshold viral copies/mL in blood or log10 drop in viral load, and improvement in or preservation of CD4+ T-lymphocyte count and/or percentage. These laboratory values are assessed at baseline and after a defined duration of therapy mostly ranging from 24 to 48 weeks. Despite significant differences between children and adults in immunologic function and response to HIV, thresholds for defining immunodeficiency and severity of viral load are similar, except for higher absolute CD4 cell counts in children < 5 years of age. For this reason, the pharmacokinetic (PK) and pharmacodynamic (PD) targets for ART have been derived from adult data, and pediatric ART studies, which have always followed the adult drug approval, have aimed to meet the same PK and PD targets.

Limited data on the relationships between ART PK and long-term toxicity in children, particularly in relationship to chronic inflammation, development of cardiovascular disease and the metabolic syndrome associated with HIV and ART in adults complicates the choice of pediatric ART. Moreover, other significant factors such as drug-drug interactions, high inter-and intra-individual variability in the PK and PD of many ARV drugs, and limited knowledge about PK/PD relationship of ARV drugs in pediatric patients all pose substantial challenges to selecting the most reliable therapeutic targets for ART in children. In this manuscript we will review the role of the PK and PD factors of the ARV drugs in the outcome of ART in pediatric and adolescent patients with HIV infection.

Therapeutic targets of different classes of ARV drugs

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Because of the extensive intracellular metabolism of NRTIs, the relationship between plasma NRTIs concentrations and virologic and immunological outcomes are not well defined in adults and children. However, a few pediatric studies suggest a potential role for the plasma exposure in defining virologic outcome of zidovudine (ZDV), didanosine (ddI) and tenofovir (TFV) [7-9]. The relationship between virologic outcome and intracellular concentrations of the NRTIs triphosphate metabolites has been suggested to be significant [10], though, the measurement of intracellular NRTIs triphosphate metabolites clinically has not been practical due to cost and labor considerations.

Exposure to NRTIs has been associated with hematologic (ZDV, emtricitabine [FTC], lamivudine [3TC]), metabolic (ddI, stavudine [d4T]), neurologic (ddI, d4T), renal (TFV) and bone (TFV) toxicities, particularly in younger children and infants with in utero and postnatal exposure [11, 12]. Few studies linked the NRTIs related toxicities with the levels of ARV exposure, while length and dose of NRTI therapy has both been identified as possible factors [13, 14]. The most commonly used strategy to address NRTI-associated toxicity is close monitoring and change of NRTI therapy if sufficient toxicity is detected [15]. Monitoring includes repeated laboratory evaluations, but it

must be recognized that while many of them (e.g. blood cell count and urine analysis) are available worldwide, others (e.g. measurement of bone mineral density or plasma lactic acid) are costly and are severely restricted in resource-limited settings.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Among all ARV drugs, first generation NNRTIs efavirenz (EFV) and nevirapine (NVP) have the best defined relationship between plasma concentrations and efficacy and toxicity. Long-term virologic suppression of HIV has been associated with maintenance of trough plasma concentrations (Cmin) above 1,000 ng/mL for EFV and 3,000 ng/mL for NVP, with some pediatric and adult studies suggesting the need for higher EFV (1,900 ng/mL) and NVP (> 4,300 ng/mL) efficacy troughs to achieve faster virologic suppression and avoid the emergence of resistance [16-18]. Achieving efficacy concentrations for NNRTIs is most important during the first weeks and months of therapy. It becomes less relevant in later stages of therapy, since high-level single mutation resistance to the first generation NNRTIs cannot be overcome by increasing the exposure and dose.

The second generation NNRTI, ETR recently received FDA approval for use in treatment-experienced children and adolescents over the age of 6 years, with limited data on the drug exposure and effect and toxicity relationships in children [19]. In adults, decreased ETR exposure has been associated with a lower virologic response rate [20]. Another second-generation NNRTI rilpivirine (RPV) is not currently approved for the use in children.

Most significant NNRTI-associated adverse effects are in the central nervous system (CNS), including insomnia, dizziness, and agitation, which can be observed in up to 25% of children and adolescents on EFV-based ART. EFV CNS toxicity has been linked to the EFV plasma exposure with Cmin plasma concentrations > 4,000 ng/mL in adults and children, and studies have suggested the usefulness of the TDM and dose adjustment to decrease high exposure and intensity of CNS side effects [18, 21]. On the contrary, another common side effect of the first generation NNRTIs such as EFV and NVP associated skin rash, and NVP associated hepatotoxicity have not been shown to be related to NNRTI plasma concentrations.

Several pediatric studies have raised concerns about high variability of EFV plasma exposure in children with currently approved EFV dosing, primarily with regards to sub-therapeutic concentrations [22]. Taking into consideration the strong effect of cytochrome P450 (CYP450) 2B6 516T>G polymorphism to increase the plasma exposure of the first generation NNRTIs in children and adults and high prevalence (15%) of these slow type EFV metabolizers among people of Black race, the most affected by HIV epidemic, suggestions regarding the use of therapeutic drug monitoring (TDM), pharmacogenetic screening and individual dose adjustment in pediatric and adolescent patients on EFV therapy have been made [23-26].

Protease Inhibitors (PIs)

Relationships between the exposure to the PIs and their efficacy have been established for the majority of the drugs in this class. The target Cmin to achieve virologic suppression of the wild type HIV has been established for atazanavir (ATV), darunavir (DRV), FPV, indinavir (IDV), lopinavir (LPV), nelfinavir (NFV), saquinavir (SQV) and tipranavir (TPV) in adults, and have been confirmed in several pediatric studies [27-34]. For most PIs, except for NFV, the target plasma Cmin is established for the PI when used with low-dose "boosting" RTV, although for ATV both boosted and unboosted efficacy Cmin in children and adults are available [35]. Most importantly, the pediatric studies of the PK/PD targets of the PIs have raised the concerns for sub-therapeutic drug exposure of the majority of PIs dosed without RTV. As a result, all PIs, except for NFV, are recommended to be used only with boosting RTV, even in treatment-naïve children and adolescents younger than 18 years of age [11].

Unlike NNRTIs, the majority of PIs acquire ARV resistance through sequential, multiple mutations. For this reason, several adult and pediatric studies suggest considering increased PI dose in treatment-experienced patients in order to achieve the higher efficacy Cmin necessary to produce virologic suppression of HIV with decreased ARV sensitivity compared to the wild type virus [35-37]. Moreover, several additional therapeutic targets incorporating both patient-specific drug exposure and HIV susceptibility have been developed to improve predictions and outcome of virologic suppression. Among those are inhibitory quotients (IQ) measuring the relationship expressed as the ratio between Cmin and the virologic susceptibility. The virologic susceptibility denominator can be represented by the inhibitory concentration (IC)

required to suppress the viral replication in vitro by 50% (IC50) for phenotypic IQ, fold-change in virtual IC50 derived from the HIV genotype multiplied by a reference wild-type protein-adjusted IC50 as the measure of viral susceptibility for virtual IQ, and the number of resistance-associated mutations for genotypic IQ. Further evaluation of the patient-specific IQ divided by a reference IQ calculated as the ratio of typical Cmin and wild type viral IC50 is defined as normalized IQ [12]. Finally, another tool to predict the virologic response to specific ARV drugs (including PIs) has been introduced and has been defined as the instantaneous inhibitory potential (IIP) [15]. IPP measures ARV activity through the slope of the dose-response curve, directly quantifying the log inhibition of single-round infectivity at clinical concentrations. Although, to date limited quantitative analysis has not demonstrated superiority of the IPP to the IQ, evaluation of the dose-response curve slope for various ARV drugs deserves further investigation [14, 38].

Various IQ targets have been proposed for APV, FPV, ATV, DRV, IDV, LPV, SQV, and TPV [12]. The clinical usefulness of this approach, however, is restricted due to the limited data on their clinical application, lack of standardized methods for calculations, high intra- and inter-patient variability in the PK of ARV drugs, variability in adherence to ART and most importantly very limited experience and expertise in combining the virologic with pharmacologic data for the therapeutic dose adjustment. Nevertheless, with the higher threshold for the development of viral resistance in the majority of the PIs, TDM and dose adjustment to meet the efficacy concentration or IQs of PIs are considered throughout the length of PI-based ART.

Except for poor palatability (LPV/RTV, RTV in liquid formulation) and gastrointestinal intolerance (most commonly LPV/RTV, RTV), the PIs are usually well tolerated by children and adolescents. The concerns for adverse effects in pediatric HIV care are focused on PI-associated changes in lipids and the unknown long-term effects of elevated cholesterol and triglycerides during childhood on the development cardiovascular disease in adulthood. No relationship between the PK parameters of the PIs and hyperlipidemia has been established to date. Most importantly, addressing hyperlipidemia in children remains a difficult task as the data on the use of diet and statins in children are limited. For IDV, one of the two PIs not approved for pediatric use, however, the relationship between PK parameters and drug associated toxicity (nephrolithiasis) has been suggested in adults [39]. The relationship with the drug PKs has also been suggested for ATV associated hyperbilirubinemia in adult studies [40]. Because ATV associated hyperbilirubinemia is generally well tolerated in children and adults, and does not require treatment interruption; TDM and ATV dose adjustment have not been considered for this purpose.

As with the first generation NNRTIs, the pharmacogenetic profile has been shown to affect PI plasma exposure. PIs are metabolized primarily by CYP450 3A4 with contribution of CYP2C19 and CYP2D6 for certain PIs. Polymorphisms of CYP3A4 have been shown to affect the systemic exposure and virologic response of certain PIs, such as IDV where CYP3A4 1B*/1B* genotype was associated with reduced peak (Cmax) and Cmin concentrations [41]. In children, polymorphism in CYP2C19 681G>A has been reported to affect the ratio of NFV with its metabolite M8 and virologic response [42]. In addition to CYP450, drug transporters have been shown to affect the disposition of PIs and influence the levels of systemic exposure in children and adults. The multi-drug transporter (MDR)1 3435C>T polymorphism increases plasma NFV concentration by reducing clearance in pediatric patients [43]. MDR1 3435T>C polymorphism also affects the PK of ATV and has been linked to the odds of developing exposure-associated ATV induced hyperbilirubinemia [40]. Another drug transporter organic anion transporting polypeptide (OATP) SLCO1B1 521T>C polymorphism has been shown to significantly increase LPV exposure in children and adults [44]. Nevertheless, despite the evident effects of drug transporter polymorphisms on the PK of PIs, no significant association has been reported with the virologic outcome [41].

Entry Inhibitors (EIs)

As the only ARV drug administered by subcutaneous injection, the fusion inhibitor enfuvirtide (T-20) has limited clinical application in pediatric practice and is reserved for salvage ART regimens with limited choice of active drugs. To date, no data on the relationship between level of exposure and the efficacy and toxicity of T-20 have been reported in adults or pediatric patients [45]. The non-competitive CCR5 inhibitor maraviroc (MVC) is not yet approved for use in pediatric patients. For future consideration of therapeutic targets of the CCR5 inhibitors, it is important to

recognize, however, that while the relationship with plasma drug concentration is important for the ARV drugs targeting the virus, different parameters may affect the efficacy of the CCR5 antagonists targeting the host cells. For MVC, the receptor occupancy in vivo has been suggested as a predictor of efficacy. Despite the fact that this approach did not receive favorable assessment in early evaluation, search for the different approach to the exposure/effect evaluation for this class of ARV drugs continues [46]. No concentration-adverse effect relationships have been reported for MVC and T-20.

Integrase Inhibitors (IIs)

The viral integrase inhibitor RAL has become a well-accepted ARV drug in adult and adolescent practice and was recently approved by FDA for use in children > 2 years of age. As with other ARV drugs, the dose selection was based upon achieving adult target PK parameters, i.e. geometric mean area under the time-concentration curve (AUC) of 14-25 mcM*h and Cmin > 13 ng/mL [47-49]. No RAL concentration/adverse effect relationships have been reported to date. Pediatric data on the DTG are limited to the 23 adolescent patients > 12 years of age used for FDA approval. Although RAL and DTG are primarily metabolized by glucuronidation via uridine 5'-diphospho-glucuronosyltransferase (UDP)-glucuronosyltransferase 1A1 (UGT1A1), to date no significant effect of UGT1A1 polymorphism on the PK and PD of RAL or DGT has been reported [50].

Drug-drug interaction and therapeutic targets of ART

Drug-drug interactions play a significant role in pediatric and adolescent ART, both within the ARV drug combinations and with concomitantly administered medications. Among all ARV drugs, NRTIs create the least concern for significant drug interactions with the most significant PK/PD effect of the co-administration of TDF and ddI, which significantly increases ddI plasma concentrations, increases the risk for associated toxicity, and produces declines in CD4 cell counts despite virologic suppression. Equally, contraindicated is the co-administration of ZDV with d4T, which competes for phosphorylation by the cellular enzyme (thymidine kinase) resulting in ZDV decreasing the phosphorylation of d4T to its active triphosphate form [51-53].

Because the NNRTIs and PIs are extensively metabolized by CYP450 enzymes and their disposition (PIs) depends on the function of multidrug transporters (MDR and OATP), these classes of ART represent a significant challenge for managing drug-drug interactions with other ARV drugs and therapeutic agents. With the introduction of newer ARV drugs into clinical practice in recent years, substantial amounts of new data have arisen about the interactions between the second generation NNRTIs, RAL and MVC with NRTIs and first generation NNRTIs with PIs. Very few studies have been published on ARV drug interactions in children, and the majority of pediatric HIV experts use the adult data to guide the choice of the therapy. Such an approach may not account for significant developmental changes in PK/PD associated with the child's growth and maturation. A recent study in pediatric patients has reported significant decreases in DRV and ETR exposure in children and adolescents (6-20 years of age) compared to adults when the drugs are administered together [54]. Despite maintaining the 90% confidence interval (CI) for DRV AUC close to the lowest range, the 90% CI for DRV Cmin was reported to be significantly below the lower limit of the therapeutic range. The 90% CI for ETR AUC and Cmin both were reported to be significantly below the lowerlimit of the target range [54]. These data highlight the contribution of drug-drug interactions or age-related changes in PK to the ARV exposure and the importance of conducting specific PK/PD evaluations of the individual drugs and probable drug-drug interactions in HIV-infected children and adults.

Among many important drug-drug interactions with ART, the most relevant to HIV-infected children worldwide arise from the need to treat concomitant tuberculosis (TB) and malaria infections. The data on drug interactions between ARV drugs and anti-tuberculosis and anti-malaria drugs have been very limited in pediatric populations and have just started to emerge in recent years. We summarized the most important data on important drug interactions between ARV and anti-TB and anti-malaria drugs in **Tab. 1**.

Among anti-TB drugs rifampin has the strongest potential for interactions with ART. Because rifampin is a potent inducer of many drug-metabolizing enzymes, it significantly lowers the concentrations of concomitantly administered drugs that are substrates for the same enzymes. Pre-dose plasma trough concentrations of PI LPV, a substrate of CYP3A4, are 90% lower when rifampin is

co-administered together vs. with LPV/RTV administered without rifampin. This drug interaction is even more intriguing, taking into consideration that LPV is co-formulated with low dose RTV, a CYP3A4 inhibitor, and suggests that the effect of rifampin on LPV exposure may be chiefly related to induction of gut P-glycoprotein and CYP3A4 [55]. Increasing RTV dose and, therefore, RTV and LPV exposures, have been shown to overcome the effects of rifampin on LPV PK (**Tab. 1**). This adjustment may lead to increased hepatotoxicity in adults; however, it appears to be well tolerated by children [56].

Rifampin also lowers concentrations of another PI, ATV. Contrary to LPV/RTV, no ATV regimen with or without RTV can overcome this induction of ATV metabolism. The dose of ATV/RTV 300/100 mg once daily, and ATV (without RTV) 300 mg or 400 mg twice daily all resulted in sub-therapeutic ATV plasma Cmin < 150 ng/mL [57, 58]. Moreover, increasing the dose of ATV/RTV to 300/100 mg of RTV twice daily resulted in significant increased gastrointestinal toxicity (vomiting) and hepatotoxicity in the first three study volunteers, prompting early termination of the approach and recommendation against the concomitant use of ATV and rifampin [59].

The concentrations of other PIs are equally and markedly lowered by rifampin, but these interactions have not been studied in children, and no evidence-based information is available on how to manage such interactions in pediatric populations. Consultation with an expert in pediatric clinical pharmacology and TDM is required before prescribing, as rifampin is currently contraindicated for the co-administration with all PIs.

Table 1. ARV interactions with anti-tuberculosis and anti-malarial drugs.

ARV Drug	ARV Drug[a]	Comments/Recommendations
LPV/RTV	**Rifampin** [55]	**LPV:RTV = 4:1 (standard formulation)[b]** 3.0-5.9 kg: 52 mg/kg q12h or 27 mg/kg q8h 6.0-9.9 kg: 40 mg/kg q12h or 21 mg/kg q8h 10.0-13.9 kg: 35 mg/kg q12h or 20 mg/kg q8h 14.0-19.9 kg: 30 mg/kg q12h or 18 mg/kg q8h
		LPV:RTV = 1:1 (extra RTV, "Super-Boosting")[b] 3.0-5.9 kg: 22 mg/kg q12h 6.0-9.9 kg: 16 mg/kg q12h 10.0-13.9 kg: 14 mg/kg q12h 14.0-19.9 kg: 12 mg/kg q12h
ATV, ATV/RTV	**Rifampin** [57-59]	**Adults:** Sub-therapeutic ATV with standard RTV-boosted or unboosted regimens and unacceptable toxicity with twice-daily RTV-boosted ATV. Avoid this combination.
NVP	**Rifampin** [60, 61]	**Age 0-3 years:** 58% reduction in NVP AUC. No dose recommendations available. **Age 4-12 years:** Minimal or no reduction in NVP AUC. No NVP dose change suggested. **All ages:** Consider therapeutic drug monitoring to manage this interaction.
EFV	**Rifampin** [56, 65, 76]	**EFV dose adjustment is not recommended.** The standard EFV dose may provide low exposure with the Cmin < 1,000 ng/mL associated with virologic failure in as many as 40% of children. Therapeutic drug monitoring should be strongly considered.
LPV/RTV	**Artemether/Lumefantrine** [67]	LPV/RTV lowered artemether concentrations in adults and raised lumefantrine concentrations. Significance and management is unknown.
LPV/RTV, ATV/RTV, EFV	**Atovaquone/Proguanil** [68]	All ARV drugs lowered both anti-malarial drugs in adults. Significance and management is unknown.
LPV/RTV	**Quinine** [69]	LPV/RTV lowered quinine exposure in adults. Significance and management is unknown.

[a]References for the recommended doses of the concomitant drug.
[b]The following recommendations are derived by population modeling and simulation based on data from 74 children aged 6 months to 4.5 years, 15 of whom had intensive PK sampling on double-dose standard formulation LPV/RTV, and 20 of whom received extra RTV in an LPV:RTV ratio of 1:1. There are no published recommended doses for children outside of these age/weight ranges. These recommendations have not been prospectively validated.

For the NNRTI NVP, the data on interaction with rifampin in children is contradictory. Oudijk J.M. et al. reported that dose-normalized NVP AUC in 21 children < 3 years of age with concomitant rifampin administration was 59% lower compared to the AUC in 16 children without rifampin therapy, and the Cmin was < 3,000 ng/mL in 52% of the children in rifampin group, compared to none of the controls [60]. However, another pediatric study by Prasitsuebsai W. et al. among older children found no difference in NVP AUC when co-administered with rifampin [61]. The median duration of concomitant HIV/TB therapy in that study was 21 weeks, which may have obscured rifampin-mediated induction of NVP metabolism in early stages of concomitant therapy and allowed for NVP to achieve sufficient levels of auto-induction of CYP3A4 to overcome the rifampin-induced effect. The lack of clear evidence for rifampin lowering NVP exposure also exists in adults, although the package insert for NVP recommends against co-administration of rifampin with NVP. A recent prospective study in HIV-infected adults on NVP with and without concomitant rifampin therapy, however, showed no difference in the rates of virologic suppression (< 50 copies/mL) after four years with both groups receiving the standard recommended NVP dose of 200 mg twice daily [62]. Despite these encouraging adult data, caution must be exercised in dosing pediatric patients (particularly young children), since 59% reduction in NVP AUC with co-administration of rifampin is significantly lower than the average 42% reduction reported for adults receiving the combination of both drugs [63]. If NVP is otherwise indicated in a child receiving rifampin, TDM is strongly encouraged.

Similar to NVP, the length of concomitant exposure appears to affect the degree of rifampin induced decrease in the exposure of another NNRTI EFV. In a prospective study of HIV-infected adults, patients receiving concomitant therapy with EFV and rifampin had significantly lower EFV plasma concentrations after 4 weeks of therapy compared to those who were receiving EFV-based ART only, with the similar EFV exposure between both groups reported by week 16 of joint therapy [64]. The auto-induction of CYP2B6 by EFV after prolonged exposure may have been roughly equivalent to the initial induction produced by rifampin. As one might expect, both rifampin- and auto-induction effects were blunted in the intermediate and slow CYP2B6 metabolizer genotypes.

In children, there may be no significant difference in EFV exposure with rifampin therapy. In a study of 15 children who were sampled at ≥ 4 weeks on concomitant EFV/rifampin therapy and at ≥ 4 weeks after discontinuation of rifampin, the median EFV Cmin was similar during both measurements (830 ng/mL vs. 860 ng/mL; p = 0.125) [56]. More recently another pediatric study in a larger cohort of 40 co-infected children reported lack of significant effect of rifampin on EFV exposure [65]. Increased EFV concentrations were observed in children with slow CYP2B6 genotype, and the authors suspected the inhibition by concomitant isoniazid of accessory EFV metabolizing pathways as the cause for this change in EFV exposure. Together these studies suggest that only fast metabolizer type CYP2B6 patients are likely to experience an early decrease in EFV concentrations due to rifampin induction of CYP2B6. Even in patients not receiving rifampin, the auto-induction by EFV itself will "catch up" to the degree of induction that would have been seen with rifampin somewhere between one to four months after concomitant EFV therapy. Although the Sustiva package insert recommends a 200 mg increase in dose for adults receiving rifampin, currently available pediatric data do not support the use of increased EFV dosing with concomitant rifampin therapy in children [65].

No data on the PK changes as a result of drug-drug interactions between ARV and anti-malarial drugs have been reported in children. A recent study on the potential for a PD interaction between artemether-lumefantrine and LPV/RTV-based ART reported a significant decrease (41%) in incidence of malaria in the group of children (2 months to 5 years of age) on LPV/RTV-based ART compared to NNRTI-based ART suggesting the potential for the significant reduction in the risk of recurrent malaria associated with LPV/RTV exposure or the interaction between LPV and malaria and anti-malaria therapy [66]. The adult data on the PK parameters with concomitant anti-malaria treatment and ART suggest the potential for the strong effect by PIs and particularly RTV. In a study of 29 HIV-infected, *P. falciparum* smear-negative Ugandan adults who were given one dose of artemether/lumefantrine, 13 on stable LPV/RTV therapy had 43% reduction in AUC and 50% reduction in Cmax of artemether compared to 16 patients not receiving LPV/RTV [67]. In contrast, the lumefantrine exposure in the LPV/RTV group was significantly increased, with 2.8-fold higher Cmax and 4.6-fold higher AUC. Although both

drugs are metabolized by CYP3A4, artemether is also metabolized by numerous other CYP450 enzymes that are induced by RTV, which may account for these discordant effects by RTV on two anti-malaria drugs.

Another study examined the effect of exposure to single dose atovaquone/proguanil in HIV-infected patients on ART with LPV/RTV, ATV/RTV or EFV in comparison with healthy volunteers [68]. The geometric mean ratio (GMR) (95% CI) for atovaquone AUC in the HIV-infected patients relative to controls was 0.25 (0.16-0.38) for those on EFV, 0.26 (0.17-0.41) for those on LPV/RTV, and 0.54 (0.35-0.83) for those on ATV/RTV. The Cmax atovaquone concentrations were similarly reduced. Proguanil exposure was also reduced, but to a lesser degree – about 40% for all three ARV groups.

Another anti-malaria drug quinine was studied in combination with LPV/RTV in HIV-negative adult volunteers, who received a single dose of quinine on day 1 and 15, and LPV/RTV on days 4-17. The quinine exposure was significantly decreased with GMR for free quinine AUC at 0.64 and GMR for 8 hour Cmin at 0.33 in combination with LPV/RTV compared with quinine alone, indicating that LPV/RTV lowered the free quinine exposure [69]. The effect of LPV/RTV on free 3-hydroxyquinine active metabolite of quinine were similar. LPV/RTV PK were unaffected by quinine.

Multiple other drugs such as antiacids, antifungals, anticonvulsants, antibacterial and antiviral agents commonly used in pediatric practice have a strong potential to affect or to be affected by the co-administration with ARV drugs. The potential for drug-drug interactions should be always evaluated in combination with ART prior to the choice of ART, anti-TB, malaria or any other therapy in co-infected pediatric patients. One of the most accessible and easily available resources to obtain up to date information on multiple drug-drug interactions for all ARV drugs and multiple pharmacologic agents is available at the website: http://www.hiv-druginteractions.org. The program has been developed and is maintained by the well established group of pharmacology experts from the University of Liverpool. The website features searchable tables of all currently known or suspected drug interactions between ARV drugs and multiple pharmacologic agents and is continuously updated with all relevant information from meetings and publications. It also exists in the form of applications for the diverse number of mobile electronic devices.

TDM of the therapeutic targets of ART

To ensure that the therapeutic targets of ART are met, one must achieve desired ARV drug concentrations with minimal exposure-related toxicity. TDM can serve as an efficient tool in attaining this goal. Consideration of TDM in pediatric HIV practice is supported by multiple reports of suboptimal drug exposure with standard recommended dosing and difficulties of eliciting the comprehensive adherence evaluation in children and adolescents [56, 70]. Most importantly, limited data on the PK and PD of ART in children, and significant developmental, physiological, psychological and social changes throughout childhood and puberty argue for strong consideration of TDM in pediatric HIV practice.

TDM of pediatric and adolescent ART is currently recommended in several clinical scenarios summarized in **Fig. 1**. Evaluation of ARV drug concentrations can be helpful when clinical responses are different from what is desired and no explanation is readily available to justify the difference in response. Another significant application of TDM is related to ART failure, particularly in the clinical settings where few alternative ARV drugs or preparations are available such as in a young child or handicapped older child with multiple resistance mutations who is unable to swallow the tablets. Increasing ARV exposure with partial viral sensitivities to meet higher plasma concentrations for the new efficacy PK threshold may be the sole option to optimize the ART in this scenario. Investigating the true picture of adherence in cases of undisclosed adherence barriers may be very useful, particularly in adolescent patients or younger children with multiple caregivers. Moreover, similar to adults, pediatric and adolescent patients are exposed to multiple drug-drug interactions with other drugs used for co-morbidities, such as TB and malaria, and for other purposes such as contraception in adolescents, all with potential for affecting ARV and/or other drug exposure. Finally, administration of ARV drugs to young children frequently requires creativity in mixing them with different foods and liquids, which increases the risk of altered absorption and concentrations of ARV drugs.

Realistically, application of TDM of ART in clinical practice has multiple barriers including

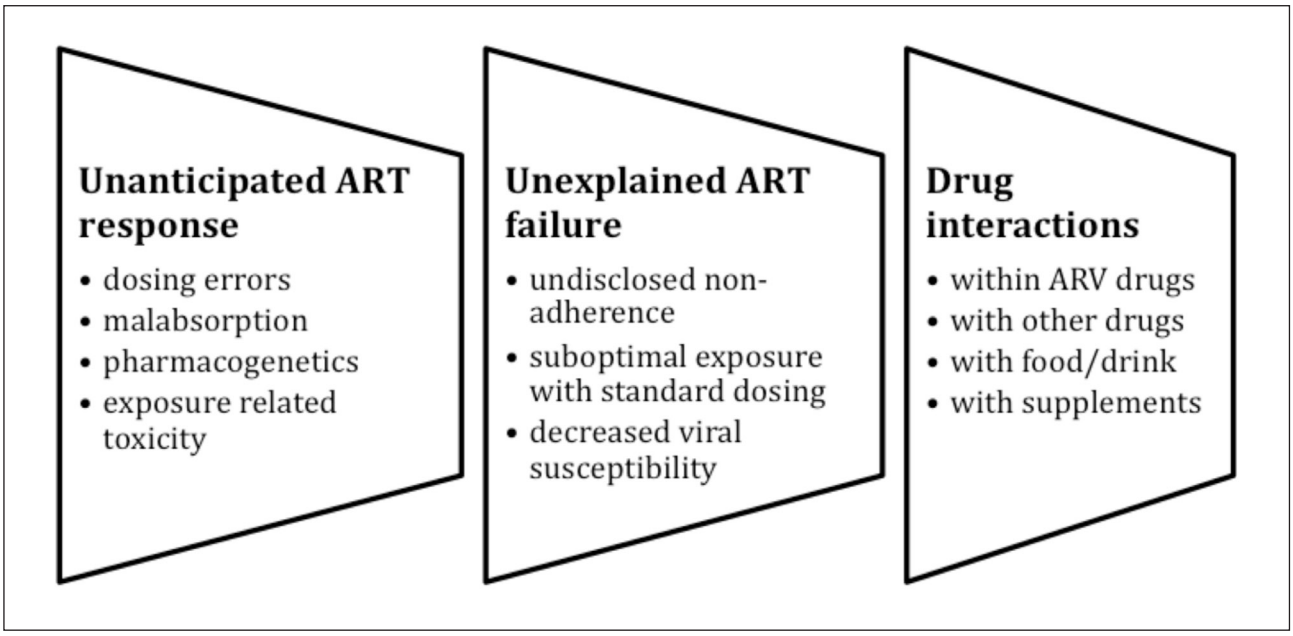

Figure 1. Indications for therapeutic drug monitoring (TDM) of antiretroviral therapy (ART) in pediatric and adolescent patients.

availability of the ARV assays, difficulties in collecting timed blood samples, prolonged time to obtaining the results, limited availability of the pharmacologic pediatric expertise, and cost and reimbursement considerations. Although several pediatric studies and case reports support the usefulness of TDM of ART in children and adolescents [18, 23, 37, 71-73], the data on the clinical application of TDM in pediatric HIV practice remain limited. Consultation with a quite limited pool of experts in pediatric HIV clinical pharmacology is required to obtain the guidance to the decisions about when to obtain samples for TDM, to interpret the PK data and to evaluate the need for dose adjustment. Despite high requirements for the successful TDM of ART, existing data and clinical experience suggest that through targeted ARV concentrations clinical responses can be improved with increased or modified doses in children and TDM should remain as a potentially useful clinical tool to pediatric and adolescent HIV specialist.

Conclusions

Increased manufacturing and approval of pediatric ARV drugs has significantly improved access to ART among children and adolescents worldwide reaching currently almost half a million HIV-infected children. This number, however, represents only a small proportion of the children in need of ART, and close to 2 million children remain in need of ART therapy as of December 2010 [74, 75]. With ongoing international efforts to provide ART coverage for every infected child, the number of children and adolescents on ART will continue to grow in the coming years reaching millions of pediatric patients worldwide.

With such large and prolonged exposure of growing and developing humans to the multi-drug ART, our ability to administer the most effective, safe and least toxic combination of ARV drugs in children and adolescents becomes crucially important. In addition, the importance of optimal dosing regimens in prevention and/or limiting HIV drug resistance cannot be overemphasized. Better understanding of the differences in therapeutic targets between children and adults and the changes in response to ART throughout the different stages of development from infancy to adulthood are needed to achieve the maximal benefit of managing the pediatric and adolescent with HIV infection.

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Declaration of interest

The Authors declare that they have no financial conflicts of interest.

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