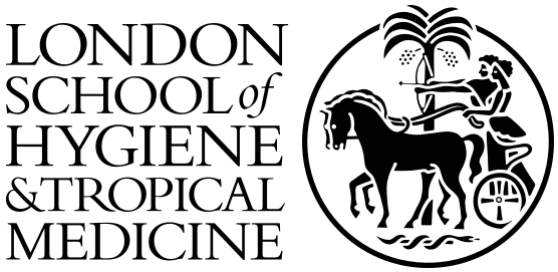

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Optimizing Pediatric Dosing Recommendations and Treatment Management of Antiretroviral Drugs Using Therapeutic Drug Monitoring Data in Children Living With HIV

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Introduction: This review summarizes the current dosing recommendations for antiretroviral (ARV) drugs in the international pediatric guidelines of the World Health Organization (WHO), US Department of Health and Human Services (DHHS), and Pediatric European Network for Treatment of AIDS (PENTA), and evaluates the research that informed these approaches. We further explore the role of data generated through therapeutic drug monitoring in optimizing the dosing of ARVs in children.

Methods: A PubMed search was conducted for the literature on ARV dosing published in English. In addition, the registration documentation of European Medicines Agency and the US Food and Drug Administration for currently used ARVs and studies referenced by the WHO, DHHS, and EMA guidelines were screened. Resulting publications were screened for papers containing data on the area under the concentration–time curve, trough concentration, and peak concentration. Studies with enrolled participants with a median or mean age of ≥18 years were excluded. No restriction on publishing date was applied.

Discussion and conclusion: Pediatric ARV dosing is frequently based on data obtained from small studies and is often simplified to facilitate dosing in the context of a public health approach. Pharmacokinetic parameters of pediatric ARVs are subject to high interpatient variation and this leads to a potential risk of underdosing or overdosing when drugs are used in real life. To ensure optimal use of ARVs and validate dosing recommendations for children, it is essential to monitor ARV dosing more thoroughly with larger sample sizes and to include diverse subpopulations. Therapeutic drug monitoring data generated in children, where available and affordable, have the potential to enhance our understanding of the appropriateness of simplified pediatric dosing strategies recommended using a public health approach and to uncover suboptimal dosing or other unanticipated issues postmarketing, further facilitating the ultimate goal of optimizing pediatric ARV treatment.

Key Words: pediatric, drug dosing, therapeutic drug monitoring, HIV, antiretroviral therapy

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INTRODUCTION

An estimated 1.8 million children younger than 15 years are living with HIV worldwide. The majority are living in low- and middle-income countries (LMICs).[1] The use of combination antiretroviral therapy for the treatment of pediatric HIV infection has markedly reduced mortality among children and adolescents infected with HIV.[2,3] Early initiation of antiretroviral treatment (ART) assures maximal suppression of HIV replication, reduces the viral reservoir, and helps

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to preserve immunologic function allowing for normal growth and development in pediatric patients.[4–6] Therefore, all current guidelines recommend to start ART in children living with HIV as early as possible, regardless of disease progression or immunologic status.[7] Currently, ART for children consists of a combination of 3 drugs from at least 2 different classes of antiretrovirals (ARVs): 2 nucleotide or nucleoside reverse transcriptase inhibitors (NRTIs) combined with a third agent, a boosted HIV protease inhibitor (PI), a nonnucleoside reverse transcriptase inhibitor (NNRTI), or an integrase strand transfer inhibitor (InSTI). Each class of ARVs targets different steps of the viral replication cycle.

Optimal ART successfully suppresses viral replication without causing side effects. This is achieved by administering the correct dose to ensure safe and therapeutic plasma concentrations. Ideally, a dose of a drug provides drug levels in the target range in all patients, regardless of age and weight, which is challenging to achieve across the pediatric age continuum.

Historically, the development and implementation of pediatric ART has been slowed by the lack of evidence from safety and dose-finding trials for child-appropriate ARV dosages and formulations already approved in adults. First, the availability of pediatric formulations for young children is a major barrier for drug development. Second, until recently, a recommended approach was to conduct the dose-finding studies in a staggered way from older to younger children, which led to a substantial delay for drug development in children. Only 25% of ARVs licensed for adults by regulatory agencies such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) are approved for treating children younger than 2 years.[8] For children living in a LMIC, availability of these drugs is further hampered by the issues of cost and procurement as well as the challenging administration and storage requirement of some drugs. Furthermore, recent data indicate significant rise in viral drug resistance to currently used NNRTIs among children, which is rapidly rising because of acquisition of the resistant viral strains from their mothers, selection of drug resistance as a result of exposure to maternal ARVs or postnatal prophylaxis, as well as suboptimal dosing and poor adherence.[9] Newer ARVs are not widely available for children, and therefore, therapy options are limited.

Based on the mechanism of action of ARV drugs on viral replication, the same exposure–response or pharmacokinetic–pharmacodynamic (PK–PD) relationship can be assumed for all age groups.[10] Therefore, provided PK exposures can be achieved similar to adults; PK and safety trials in children are considered sufficient to support regulatory approval and use of ARVs in children.[10]

The absorption, distribution, metabolism, and excretion of drugs in neonates, infants, and children are all affected by changes in body size and maturation processes.[11–15] Although knowledge and study methods in pediatric pharmacology have been improving, and requirements for pediatric dose–finding studies for ARV drugs have become more stringent, pediatric dosing of the majority of currently used ARV drugs is still based on the empirical or weight-based scaling of adult doses.[16] Maturation and development in organ function of children creates changes in drug PK, which make scaling unpredictable, especially for children younger than 2 years.[17]

Population PK (PopPK) modeling can be used to approximate the effect of maturation factors on drug PK in children, but without data from children, modeling involves extrapolating from other populations and assumes equivalent PK processes in the intended population. When data in children are available, population modeling can be used to provide insight into the causes of PK variability within the pediatric population.

Apart from the right dose, formulations for children should be "child-friendly" to enable children to take them. Therefore, pediatric formulations primarily involve liquids or low-dose dispersible formulations, which are easy to swallow and allow for gradual dosing alterations when a child is growing. Liquid formulations, however, have excipients that can be toxic to newborns, for example, high alcohol and propylene glycol content in liquid lopinavir/ritonavir.[18] They require administrations of larger volumes and have more challenging storage and transport requirements (eg, cold chain and refrigeration). Solid preparations are generally significantly easier to handle and procure. Hence, preference is given to pediatric dispersible and solid preparations globally.[19]

International guidelines have been developed and are regularly updated using latest research results to guide clinicians on specific ARVs, formulations, and dosing for children living with HIV. The 3 guidelines that are most widely used are from the World Health Organization (WHO), US Department of Health and Human Services (DHHS), and Pediatric European Network for Treatment of AIDS (PENTA).[7,20–22] Although stringent regulatory drug approval agencies such as the FDA and EMA base their licensing generally on the same information, they do not overlap completely in their age indication and dosing guidance. As a result, European and American guidelines are not always aligned on some key points.[7,20–22] Until recently, the EMA and FDA recommended a dose stratified by age and calculated by multiplying a drug dose in milligram by the body surface area (BSA) or weight, necessitating a calculation. To simplify this approach, the WHO introduced weight-band dosing to support a public health approach and to promote scale up of pediatric ART. Weight-band dosing, however, is not without challenges. Dosing within the given weight band is static and therefore children on the extreme ends of the weight band might have higher or lower drug exposure relative to the target levels, which may affect toxicity or efficacy.

In settings where therapeutic drug monitoring (TDM) is available, it is used to make individual dose adjustments after examining the actual drug concentration achieved.[23] More recent ARVs have broader therapeutic windows with improved benefit/risk ratios and reduced intersubject variability; thus, the need for TDM of these drugs is currently limited to certain clinical scenarios. However, because larger interindividual variations in plasma concentrations are seen in children and this population is more vulnerable to drug-related adverse events, clinicians may opt to use TDM in children for clinical management when dosing uncertainties arise.[23] Drug-level results can also indicate nonadherence and can be used by health care providers to initiate additional interventions to

help those children struggling with maintaining drug adherence; however, simplified, cheaper assays are needed to move this testing outside of research settings and highly resourced facilities.[24]

To fully explore the value and potential use of TDM for validation of recommended dosing, we reviewed the evidence base for currently recommended dosing of different ARVs used in first-, second-, and third-line regimens. This review identifies knowledge gaps that, if addressed, could help improve pediatric ARVs dosing and, in turn, pediatric HIV treatment outcomes. We focus on the agents for which plasma PK parameters are used for dose-finding, and therefore, nucleoside (and nucleotide) reverse transcriptase inhibitors (NRTIs) are covered only briefly.

METHODS

We described the current pediatric dosing recommendations outlined in 3 international guidelines (DHHS 2018; WHO 2016 and 2018; and PENTA 2015),[7,20–22] and the studies that are used to inform these recommendations. For these studies, we extracted the following PK parameters: area under the concentration–time curve (AUC), plasma trough concentrations (C_{trough}), and maximum plasma concentration (C_{max}), as well as the characteristics of the studied populations.

A PubMed search was used to explore the available data on ARV dosing using the combined strategy with the key words and MeSH terms for generic names of the currently used ARV drugs and ARV classes, HIV infection, PK, and TDM (see **Search strategy**, **Supplemental Digital Content 1**, http://links.lww.com/TDM/A325 section of this review). The search was restricted to the literature published in English with no limits on publishing date. In addition, documentation publicly available through the EMA and FDA was screened and studies referenced by the above guidelines. Papers containing data on the AUC, C_{trough}, or C_{max} of currently used ARVs were considered and summarized. Trials with a median or mean age of participants 18 years or older were not included, except for reference information.

Dosing of ARVs in Children

ARV drug dosing currently recommended in children is based on varying amounts of published data. In this section, we describe individual ARVs (divided by drug class), provide an overview of pediatric PK studies and dosing strategies in children, and compare the PK parameters of the pediatric studies with adult targets for therapeutic drug concentrations.

Dosing recommendations for the currently used pediatric ARV drugs are presented in **Supplemental Digital Content 2** (see **Table 1**, http://links.lww.com/TDM/A324).

NRTIs

A dual NRTI "back-bone" remains a key component of current ARV regimens. NRTIs are prodrugs that are activated intracellularly to exert their therapeutic effect. The NRTIs presently used are abacavir (ABC), zidovudine (ZDV), lamivudine (3TC), emtricitabine (FTC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide fumarate (TAF). Although intracellular concentrations of some NRTIs were shown to be correlated with markers of therapeutic effectiveness, such as viral load decline and CD4 increase,[25] measuring intracellular concentrations of the active compound is expensive and labor intensive, and thus, these concentrations are not routinely targeted for TDM, except for research purposes. Unfortunately, dose or plasma concentration of the parent compound does not correlate well with intracellular concentration of the active form of the drug at the target site.[26–28] The dose of an NRTI does not correlate with a PK parameter that can predict efficacy; therefore, discussing the dose of NRTIs is not within the scope of this review.

One exception is made for the new NRTI "TAF," which is expected to be more widely included in upcoming treatment guidelines for children. Data on TAF are described in relation to the InSTI elvitegravir below. NRTI-approved doses are reported in **Supplemental Digital Content 2** (see **Table 1**, http://links.lww.com/TDM/A324) to provide a full overview of dosing in the current guidelines.

NNRTIs

Efavirenz

Historically, efavirenz (EFV) has been dosed in adults at 600 mg once daily (QD) with a backbone of 2 NRTIs, although a lower 400-mg QD dose is now also recommended.

A target therapeutic range for mid-dose EFV levels of >1.0 mg/L to <4.0 mg/L has been identified in adult studies. Half (50%) of adults with mid-dose levels under 1.0 mg/L experienced viral failure, whereas central nervous system side effects increased about 3-fold with EFV plasma above 4.0 mg/L.[29,30]

EFV for children has been formulated as an oral solution (30 mg/mL) or in capsules, which can be opened to deliver an adjusted dose. Bioavailability of the oral liquid relative to capsules or tablets is low at only 46.6% and has also shown to give more variable exposure. The liquid formulation is not part of the ARV guidelines anymore.[31,32]

EFV is licensed by the EMA and FDA for children aged 3 months and older weighing more than 3.5 kg and is dosed based on weight bands (see **Table 1**, **Supplemental Digital Content 2**, http://links.lww.com/TDM/A324). Nevertheless, guidelines do not recommend the use of EFV in children younger than 3 years because of highly variable PK in young children. EFV is primarily metabolized by the cytochrome-(CYP)2B6 enzyme and EFV PK is affected by polymorphisms in the CYP2B6 gene. The International Maternal Pediatric Adolescents AIDS Clinical Trials Network (IMPAACT) P1070 trial showed considerable risk of underdosing in 80% of infants and young children who were "extensive" metabolizers for CYP2B6. Alternatively, an increased dose of EFV (approximately 1600 mg × [weight in kg/70]) aimed to achieve adequate exposure for all participants in the P1070 trial, led to approximately 4-fold higher EFV exposure in the remaining 19% who were poor metabolizers, and increased their risk of experiencing EFV-associated side effects.[33] Genetic polymorphism in other EFV-metabolizing CYP enzymes, such as CYP2A6, has also shown to affect EFV PK and could potentially influence treat-

ment outcome in children.[34,35] It is not recommended to treat children younger than 3 years with EFV without CYP2B6 genotyping to guide dosing. Genotyping of CYP2B6 in older children could possibly be beneficial to evaluate the necessity for dose adjustment and to help decrease the risk of side effects and incidence of viral failure.[31,36] However, genotyping is expensive and most importantly not accessible to many clinics, in particular in LMICs, and it is rarely used in clinical practice.

Nevirapine

Despite the current global efforts to move away from nevirapine (NVP) and the desire to transition to more optimal and effective regimens, it has long been a core ARV in ART regimens in some LMICs. In adults, NVP can be administered as 200-mg tablets twice daily (BD) or 400-mg extended-release (NVP-ER) tablets QD. NVP is both a substrate and an inducer of the hepatic enzymes CYP3A4/5 and CYP2B6. To allow for autoinduction to set in, a 2-week lead-in dos of 50% of the therapeutic dose is used in adults, and this concept is also still recommended for pediatric dosing in the United States and Europe (except for neonates where no lead-in is required).[20,37]

In the presence of replicating virus, a single mutation can select for high-level resistant virus to NVP, and several studies have found association between low NVP concentrations and virological failure; therefore, achieving and maintaining therapeutic drug levels of NVP is crucial.[38] Different target plasma trough concentrations have been identified in adults ranging from 3.0 mg/L[39] to 4.3 mg/L.[40,41] The most commonly followed target is a C_{trough} of 3.0 mg/L, as this threshold was derived within the largest cohort.[39] No direct relationship was found between NVP PK parameters and NVP-associated toxicity: higher NVP concentrations are not strongly related to increased incidences of adverse events such as rash or hypersensitivity.[42]

The Verve study showed an increase in viral failure with C_{trough} levels <2.0 mg/L in adults treated with NVP-ER; therefore, NVP plasma levels of 2.0 mg/L can be considered a target for treating patients with NVP-ER administered QD.[43]

Once-daily dosing with extended-release NVP formulation is licensed in children older than 6 years after a lead-in period with a 50% dose using formulations meant for BD dosing. Giaquinto et al[44] studied the PK of the extended-release formulation in pediatric patients and showed that the median AUC and C_{trough} are comparable with the immediate-release NVP formulation.

NVP is used in children either as a prophylactic agent, in the context of perinatal transmission prevention, or for treatment. As a prophylactic agent, different dosing strategies are used with similar efficacy.[45,46] These regimens were originally designed to maintain NVP plasma concentration >0.1 mg/L throughout the period at risk of HIV exposure.[47]

Several immediate-release NVP formulations are licensed for treatment in children and they are all considered to be bioequivalent.[37] Although DHHS guidelines recommend giving NVP from birth (without the lead-in period), it is not approved for newborns younger than 15 days of life according to the current FDA-approved package insert. The current NVP dose in children is based on scaled-down adult doses. Both the EMA and FDA recommend NVP in children dosed 150 mg/m^2 BD with a lead-in dose of 150 mg/m^2 QD for 2 weeks. Dosing guidance by the WHO is based on weight bands. A modeling study by Nikanjam et al,[48] based on combined NVP PK data from a range of pediatric studies, demonstrated that WHO weight-band dosing would maintain adequate drug levels for the majority of patients similar to the FDA BSA–based dosing schedule.

Gopalan et al (the study in children 2 to <18 years) and Fillekes et al (the study in children >1 month old weighing 3 to <6 kg) found subtherapeutic NVP concentrations in up to 65% and 32% of their respective study populations in the lead-in period (see **Table 2**, **Supplemental Digital Content 2**, http://links.lww.com/TDM/A324).[38,49] In addition, starting with the full dose did not translate to increased adverse events in these studies.[38,49] This information is likely to change recommendations regarding NVP lead-in dosing in the guidelines. Predicting NVP oral clearance is even more difficult because of the impact of genotypic polymorphism in the CYP450 enzymes involved in the metabolism of NVP. For example, CYP2B6 polymorphism affects clinical outcomes in children. Children with the "extensive" metabolizer phenotype have an increased risk of being underdosed.[50]

Rilpivirine

Rilpivirine (RPV) dosed 25 mg QD is used, mostly in Western countries, as part of triple therapy with dual NRTIs in adults and adolescents. It is also increasingly used in combination with other ARV classes and as a part of dual therapy including oral and long-term injectable formulations (DTG + RPV or cabotegravir [CAB] + RPV). In combination with NRTIs, RPV should only be used in patients with initial viral loads <100,000 copies/mL. With higher initial viral loads, RPV-based ART had higher rates of virological failure compared with EFV-based ART.[51]

Target therapeutic plasma trough concentration for RPV has not been clearly defined, but lower rates of virological response have been found with median C_{trough} concentrations below 0.042 mg/L.[52] In terms of toxicity, RPV increases QT interval in a concentration-dependent manner. Clinical relevant increases in QT have been correlated with C_{max} concentrations >0.60 mg/L.[52,53]

Adult doses of RPV is approved by the EMA and FDA to use for children older than 12 years and weighing more than 35 kg with viral loads <100,000 copies/mL. In the PAINT study, 4 of 8 (50%) participants aged 12 to <18 years with initial viral loads >100,000 copies/mL did not meet virological suppression criteria versus 6 of 28 (79%) participants with initial viral loads <100,000 copies/mL, supporting the validity of this virologic cutoff in children (see **Table 2**, **Supplemental Digital Content 2**, http://links.lww.com/TDM/A324).[54]

In children aged 12–18 years, the PK parameters of RPV were similar to adults with comparable variability. The studies in adolescents did not report a correlation between dose and efficacy or toxicity. There have been no studies published yet using a pediatric RPV formulation. Further research on RPV

formulations including long-acting injectable formulations in children and adolescents is needed to guide dosing in younger children and to evaluate targets for therapy.

PIs

Atazanavir

Atazanavir (ATV) is dosed in adults QD either in combination with PK "boosters" ritonavir or cobicistat at 300/100 mg and 300/150 mg, respectively, or unboosted under restrictive conditions 400-mg ATV QD, combined with a NRTI back bone.

ATV drug monitoring is guided by trough concentrations. Trough concentrations of ATV above 0.15 mg/L are correlated with lower rates of viral failure in ART-naive patients.[55,56] Patients previously treated with PI containing ART need higher ATV trough levels for each mutation that decreases the susceptibility of the virus to ATV. A concentration of 0.23 mg/L/mutation has been correlated with higher efficacy.[57] The upper limit of treatment dose is less well defined but is determined by the rise of unconjugated bilirubin, the main adverse event caused by ATV, for which a correlation is seen with ATV C_{trough} in the range of 0.50–0.76 mg/L.[58–60] Safety data from a large cohort study on ATV/r in children also show increasing incidence and severity of hyperbilirubinemia with increasing C_{trough}.[61] Because in this case the increase in bilirubin is not a product of liver damage but rather because ATV interacts with bilirubin conjugation, this effect is benign. Advantages of therapy should be weighed against potential stigmatizing side effect of icteric eyes from an increase in unconjugated bilirubin.

In children, ATV is administered only as ATV/r and is recommended for children older than 3 months weighing >5 kg following the dosing schedule displayed in **Supplemental Digital Content 2** (see **Table 1**, http://links.lww.com/TDM/A324). ATV boosted with cobicistat has not been studied in children. Under 3 months of age, the risk of ATV-induced kernicterus increases, and ATV is thus not recommended in this age group. In a pediatric ATV dose-finding study (IMPAACT P1020; n = 195 children aged 3 months to 21 years of age), Kiser et al[62] aimed to attain ATV PK parameters similar to adults. They used a range of increasing ATV doses over an increasing range of the BSA, both with and without ritonavir boosting, and attained the target PK parameters with ATV/r for children across all studied age groups, and with unboosted ATV capsules for children 2 to <13 years. However, treatment with unboosted ATV powder formulation could not satisfy predetermined PK parameters in children aged 3 months to <13 years. This was likely a consequence of low ATV bioavailability, a faster clearance, and a wide intersubject variability in this age group.[62,63] Subsequent modeling by Hong et al[64] translated dosing based on the BSA into a dosing table based on weight bands for the capsule formulations. The PRINCE I and PRINCE II trials showed that ATV powder formulation in combination with RTV liquid in children 3 months to <11 years and weighing 5 to <35 kg dosed in weight bands reached the target drug exposure levels.[61,65,66] Results from the PRINCE I and II trials together with IMPAACT P1020 and the modeling study by Hong et al supported the FDA approval of ATV/r doses in children (see **Table 3**, **Supplemental Digital Content 2**, http://links.lww.com/TDM/A324).

Two additional studies with ATV/r in children are referenced in **Supplemental Digital Content 1** (see **Table 3**, http://links.lww.com/TDM/A324). One study investigated the dosing of ATV/r combined with TDF in Asian children living with HIV.[67] It is hypothesized that TDF decreases ATV exposure by inducing P-glycoprotein, resulting in decreased ATV bioavailability.[68] Higher PI drug levels have been reported in people of Asian origin.[69] Bunupuradah et al[67] showed that 200-mg ATV boosted with 100 mg of ritonavir within a regimen containing TDF was able to achieve ATV levels comparable with adult levels in Asian children aged 6–18 years. Another study, by Cressey et al,[70] investigated the possibility of using unboosted ATV in ART-experienced Thai children unable to take ritonavir. Doses of 400-mg and 600-mg unboosted ATV did not achieve target C_{trough} levels and were highly variable between patients. Theoretically, increasing the unboosted ATV doses further may be able to exert sufficient exposure, but this requires additional research.

The results from pediatric ATV trials displayed in **Supplemental Digital Content 2** (see **Table 3**, http://links.lww.com/TDM/A324) show the data used to inform the decision on ATV doses for the product label and in the current guidelines. It should be noted that weight-band pediatric doses are derived from doses based on the BSA in the P1020 trial and converted to weight-band dosing by modeling alone (Hong et al[64]). Thus, clinical validation of these doses is needed, which is planned in the CHAPAS-4 trial.[71]

Two separate ATV formulations are used in children: oral powder and capsules. According to the regulatory agencies, the formulations are not bioequivalent based on results of the Prince I and Prince II studies, and according to a modeling study by Hong et al, who report a modeled relative bioavailability decrease of 35% for oral powder formulation compared with the capsule formulation for children 15–25 kg.[72] This assumption is not supported by the findings from the IMPAACT P1020 trial, who show that a 150% increase of mg/m^2 dose in capsule versus oral powder resulted in a >150% increase in C_{trough}.[62] In the IMPAACT trial, these formulations result in similar exposure. However, the age and weight of these children was different between the groups.

Darunavir

In adult patients, darunavir/ritonavir (DRV/r) is dosed at 800/100 mg QD in treatment-naive or treatment-experienced patients without genotypic resistance to darunavir and 600/100 mg BD in patients with DRV-specific mutations.

No relation to clinical effect has been reported for DRV AUC or C_{trough} values, but an in vitro study by Kakuda et al[73] showed that a protein-binding adjusted plasma concentration of 0.55 mg/L exerts 50% of the maximal effect (EC_{50}) for susceptible viruses. No EC_{90} or other efficacy parameters have been reported. Mean C_{trough} for QD DRV/r in adults was 2.0 mg/L.[73] Interestingly, 50% reduced C_{trough} did not lower the

predicted mean virological response rate in the ARTEMIS trial (92.8% for >2.0 mg/L versus 93% for >1.0 mg/L), showing that a C_{trough} of 1.0 mg/L can also be adequate.

Darunavir is licensed in children older than 3 years weighing more than 10 kg. Boosted with ritonavir, it can be dosed BD or QD. Boosting DRV with cobicistat has not been studied in children and is therefore not approved by the EMA or FDA. There are multiple DRV formulations available for pediatric dosing, all considered to be bioequivalent.[74] A suspension of 100 mg/mL can be used in children from 10 kg; for children over 15 kg able to swallow tablets, tablets are available. Both the FDA and EMA approved QD dosing for children without DRV resistance–associated mutations, and BD dosing for children with DRV mutations. PENTA 2015 and DHHS guidelines recommend BD dosing for all children <40 kg (see **Table 1**, **Supplemental Digital Content 2**, http://links.lww.com/TDM/A324).

Pediatric Dosing of BD Darunavir Ritonavir

A series of trials investigated DRV dosing in children in a stepwise approach down to age of 3 years. The Delphi study investigated DRV/r BD in children 6 years or older. Stratified by weight bands, pediatric patients reached PK parameters comparable with results achieved in adult studies. Initially, a dose directly scaled down from adults was studied, but this was rejected because of inferior exposure.[75] The age limit for DRV use was lowered to 3 years based on the ARIEL study. In ARIEL, children older than 3 years and weighing >10 kg were initially dosed 20/3 mg/kg. This dose was increased to 25/3 mg/kg for children 10 to <15 kg and a fixed dose of 375/50 mg/kg was given to children 15 kg to <20 kg because low $AUC_{0\text{-}24}$ and C_{trough} were projected by a modeling study and after reviewing the week 2 safety, PK, and antiviral activity data within ARIEL. Subsequent PK analysis of the new dose revealed increased $AUC_{0–24}$ and C_{trough} levels compared with adult parameters.[76] However, no adverse events were reported when the dose was increased to 25/3 mg/kg in the ARIEL trial.[77] Eventually, FDA reviewers recommended the initial dose of 20/3 mg/kg DRV/r for children 10 to <15 kg.[76,77] This decision was based on 2 considerations (1) additional analysis of the data from the ARIEL trial showed that the exposure reached with a dose of 25/3 mg/kg DRV/r was 153% of the adult exposure; and (2) administering a dose requires an oral syringe to obtain the required volume, which is prone to mistakes and poses additional risk of high exposures. Ultimately, this means that the current FDA-licensed dose for children 10 to <15 kg is based only on 2 weeks of PK and safety data before the dose was increased in the ARIEL trial. The WHO recommends a dose of 250-mg DRV for children 10–14.9 kg (25 –16.67 mg/kg) based on modeling.[78] The EMA currently has not licensed dosing in children weighing <15 kg.

Pediatric Dosing of QD Darunavir Ritonavir

Once-daily dosing in pediatric patients has been explored in several studies (see **Table 3**, **Supplemental Digital Content 2**, http://links.lww.com/TDM/A324). QD dosing of DRV/r in children is largely based on the ARIEL study for 3 to <6 years old, and the DIONE study for 12 to <18-year-old children. Using these data, Brochot et al[79] modeled dosing for children 3 to <12 years old and provided the dosing recommendations for children 6 to <12 years old. However, the following Daphne trial reported a geometric mean AUC of only 70% of the adult levels with the suggested doses in children 12 to <18 years old.[80] Despite the lower exposures, the authors argued that the children were adequately treated given the high viral suppression rates (91% at 12 months) observed in this study and the fact that all observed C_{trough} values were well above EC_{50} for susceptible viruses, which could be considered a target level for therapy.

It must be noted that all patients in the pediatric trials of QD DRV, except in the study by Chokephaibulkit et al, had a C_{trough} above 0.55 mg/L, the EC_{50} for susceptible viruses (see **Table 3**, **Supplemental Digital Content 2**, http://links.lww.com/TDM/A324),[81] and all children had high viral suppression rates regardless of decreased AUC compared with adult AUC.[75,76,80,82,83]

Lopinavir/Ritonavir

Lopinavir/ritonavir (LPV/r) dosed 400/100 mg BD combined with 2 NRTIs can be used in adult treatment. In treatment-naive adults or adults with less than 3 relevant PI mutations, a QD regimen of LPV/r combined with an NRTI backbone can be used at 800/100 mg.

Lopinavir C_{trough} of 1.0 mg/L has been shown to give sufficient LPV exposure in ART-naive patients, and this level is used as a target for TDM in both adult and pediatric patients.[7,84] For ART-experienced patients, target trough concentrations are related to the number of mutations and are reported varying from 0.7 to 0.9 mg/L per LPV-relevant mutation.[85,86] Some studies have been conducted to determine whether the target trough level for adults can be used in pediatric therapy, but no different target has been adopted so far for treating children.[87–89]

Lopinavir/r is licensed for use in children from the age of 14 days. Owing to cardiac and metabolic toxicities as well as risk of adrenal insufficiency, children younger than 14 days should not use LPV/r.[18]

Lopinavir can be administered as liquid formulation or pediatric tablets (for children >15 kg). The tablet formulation has shown less variability than the previously used softgel capsules.[69,90] Dosing on the BSA requires calculation. To make dosing easier, weight-band–based dosing was explored by Bastiaans et al.[91]

Both 230/57.5 mg/m^2 and 300/75 mg/m^2 LPV/r doses are within the recommendations of the DHHS guideline and have shown adequate efficacy and acceptable toxicity in trials.[92–98] However, concerns have been raised on the durability of the levels of exposures achieved by the 230/57.5 mg/m^2 dose, especially in children <2 years old, for whom increased LPV clearance is observed.[99–101] Because of these concerns, 300/75 LPV/r mg/m^2 dose is recommended for treatment-experienced children of all ages; 230/57.5 mg/m^2 can be used in treatment-naive children aged >1 year.

Furthermore, Rakhmanina et al[102] concluded that the current BD LPV/r dosing strategy for naive children appears to be adequate for therapy in children infected by wild-type

virus but is unlikely to be suppressive for viruses with even mild resistance to LPV. The authors conclude that patients would benefit from TDM and resistance testing.

Once-daily dosing of LPV is not recommended in routine care of HIV-infected children. Although LPV exposure of QD LPV/r is comparable with exposures seen in adults, noninferiority of LPV/r QD was not proven to the BD regimen in a randomized controlled trial.[103–105] The KONCERT trial compared LPV/r dosed QD versus dosing BD in virologically suppressed children and reported a doubling in risk of viral failure when using a QD regimen versus the conventional BD regimen. This result appears to be primarily influenced by nonadherence and showed that a QD dosing strategy was less forgiving than the BD standard regimen. However, in a select group of adherent children and under guidance of TDM, QD dosing of LPV/r can be a valid treatment.[106]

A recent modeling study evaluated the effect of formulation and age on the exposure of LPV. A dramatic decrease in relative clearance with increasing age was noted in the first 2 years of life, and an increase in bioavailability was observed when children were switched from liquid formulation to tablet formulation, providing evidence for the need to re-evaluate current dosing of LPV in young children or perhaps change to a different formulation such as LPV/r oral pellets.[107] LPV/r oral pellets have shown to increase exposure compared with the liquid LPV/r formulation in children in the CHAPAS-2 trial and were associated with high levels of viral suppression in the LIVING study.[108,109] These oral pellets are currently approved by the WHO and the FDA under the PEPFAR program.[110,111] A novel pediatric LPV/r granule formulation is now available (40/10 mg) and actively introduced in countries while a taste-masked LPV/r granule formulation within a fixed-dose combination (FDC) with abacavir/lamivudine (4-in-1 combination) is being finalized with anticipated approval in early 2020.

InSTIs

Dolutegravir

Dolutegravir (DTG) has been at the center of attention lately because of its excellent viral outcomes, high barrier to resistance, broad therapeutic window, and relatively few drug interactions compared with PIs. DTG in adults is dosed at 50 mg QD when InSTI-naive and can be increased to 50 mg BD when InSTI resistance–related mutations are present. It is available as single strength tablets and in FDCs with ABC/3TC or TAF/FTC.

There is no consensus on the PK target related to efficacy for DTG. C_{trough} best predicted plasma viral load reduction in a 10-day DTG monotherapy study by Min et al.[112] The Emax model identified an EC_{50} of 0.036 mg/L and calculated EC_{90} of 0.324 mg/L, the latter could be taken as a cutoff for efficacy.[112] Safety data do not show a relationship with PK targets.

In children, DTG is dosed according to **Supplemental Digital Content 2** (see **Table 1**, http://links.lww.com/TDM/A324) and is licensed in Europe for children older than 6 years and 15 kg. Currently, the approved dose can be delivered using a film-coated tablet in 2 dosage forms (10 and 25 mg), and work is undergoing to test a dispersible 5-mg tablet for dosing in younger children as well as a FDC in combination with ABC/3TC.

The IMPAACT P1093 trial is an ongoing dose-finding study, evaluating the safety of DTG in children down to 4 weeks of age. Based on data from P1093, the adult dose is approved by the EMA and FDA for ART-naive and ART-experienced—but InSTI-naive—children older than 6 years weighing over 40 kg. A decreased dose of 35 mg QD is approved for children 30 to <40 kg. The EMA has also approved dosing in children older than 6 years weighing >15 kg, based on a modeling study by Sing et al informed by data from the IMPAACT P1093 trial.[113] However, the FDA concluded that the data for the lowest weight bands were insufficient to recommend the use of DTG in children <30 kg because of the scarcity of the data and lower than expected observed $C_{trough.}$

Recently, new PK information on DTG in children has become available from P1093 and ODYSSEY trials. In a nested PK study within the ODYSSEY trial aiming to simplify the dosing across the WHO weight bands, children 14 to <25 kg were dosed at 25 mg (steady-state intensive single PK curve), whereas children 25 to <40 kg had a crossover PK assessment and received a licensed dose on the first PK day and an adult dose of 50 mg on the second PK day. Participants 14 to <25 kg and 25 to <40 kg on the initial doses (PK day 1) showed lower C_{trough} levels compared with adults. However, with the increased dose of 50-mg DTG, the C_{trough} levels in children 25–40 kg increased comparable with adult reference values. Based on these results, the WHO recommended a DTG dose of 50 mg for children ≥25 kg in the revised guidelines. PK data from the Odyssey trial in children 20 to <25 kg treated with 50-mg film-coated tablets or 30-mg dispersible tablets showed exposures and trough levels comparable with adult data but with C_{max} exceeding adult reference values. Doses intended to achieve higher plasma drug levels are currently being investigated with both dispersible and film-coated tablets in younger children in the ongoing PK study in ODYSSEY.[114] Both ODYSSEY and P1093 have started enrolling children from 4 weeks; some available data are presented in **Supplemental Digital Content 2** (see **Table 4**, http://links.lww.com/TDM/A324).

Raltegravir

Raltegravir (RTG) shows good therapeutic efficacy in adults at a dose of 400 mg BD or 1200 mg RTG high-dose (two 600-mg tablets) QD.

PK targets are devised based on a number of studies with QD dosing of RTG in adults but could not be identified in studies using the registered BD dose. C_{trough} concentrations below 0.045 mg/L correlated with increased viral failure.[115] Correlations between plasma concentrations and toxicity have not been reported to date.

RTG can be used in children across all ages. Different formulations of RTG have been approved by the EMA and FDA. RTG weight-band dosing is available for children from 2 kg using granules for oral suspension, before moving on to

pediatric chewable tablets for children weighing ≥11 kg and film-coated tablets for children ≥25 kg (see **Table 1**, **Supplemental Digital Content 2**, http://links.lww.com/TDM/A324). Oral suspension has shown better oral bioavailability compared with the chewable tablets, and both formulations showed greater bioavailability compared with the film-coated tablets.[116] All formulations should be dosed according to their own specific dosing guidance as displayed in **Supplemental Digital Content 2** (see **Table 1**, http://links.lww.com/TDM/A324).[116]

In the pediatric trials (see **Table 4**, **Supplemental Digital Content 2**, http://links.lww.com/TDM/A324), the tested dosing showed mean PK parameters comparable with adult values. However, large variability in PK parameters was observed when treating children, especially with the film-coated tablets. For patients younger than 6 years, the coefficient of variation was over 200%. RTG doses for children aged 4 weeks to <18 years old were confirmed in a modeling study using the data from the P1066 trial.[117] In this study, all dosing strategies met the prerequisite PK targets. Recently, data of RTG oral granules for suspension were presented showing RTG was safe and well tolerated during the first 6 weeks of life, although a complex preparation process and increasing RTG doses to accommodate for rapidly increasing UGT1A1 metabolism is required in the neonatal period.[118] Feasibility and acceptability studies are required to evaluate the utility of these formulations in remote settings.

Pediatric RTG dosing is currently based on PK data from a limited number of children with large variability. These data are backed up with a modeling study based on the data from the same trial. Taking into account that therapeutic targets are not yet very well defined, larger and more variable cohorts should be studied to know whether these dosing guidelines ensure efficacy in children. Only about 50% of children in the P1066 trial reached a viral load of <50 copies/mL and over 70% of subjects had viral load of <400 copies/mL at 48 weeks of therapy. This difference indicates low-level viremia in some children, whether this has led to the development of resistance in these trials, has not been yet reported.[119,120] Overall, taking into account, BD dosing and low barrier to resistance RAL does not appear to be the best option for older children and adolescents. However, in view of the limited ART regimens for neonates and young children, RAL presents an important treatment option while we await dolutegravir to become available for this age group.

Elvitegravir

Elvitegravir (EVG) is dosed in adults only as part of FDC tablets that include the PK enhancer cobicistat. FDC tablets include 150-mg EVG coformulated with COBI 150 mg plus FTC 200 mg, and either TAF 10 mg or TDF 300 mg.

A target for therapy was identified based on the initial dose-finding studies by DeJesus et al.[121] A C_{trough} value of 0.13 mg/L showed an almost maximum effect based on an E_{max} model. There was no target identifiable that showed correlation with any toxicity markers.

Recently, studies have indicated that EVG can be used in children older than 6 years and weighing at least 25 kg combined with COBI and TAF/FTC at adult doses. In combination with TDF/FTC, EVG/COBI is only approved by the EMA and FDA for children older than 12 years.

There are 2 studies on PK of EVG in children reported in **Supplemental Digital Content 2** (see **Table 4**, http://links.lww.com/TDM/A324).[122] For both groups, but especially in children 6–11 years old, the AUC, C_{max}, and C_{trough} concentrations are higher than in the adult population. Moreover, trough concentrations for these children show considerable variability for both children 6–11 years old and 12 to <18 years old. Long-term safety of this combination in children still needs to be examined. Currently, only the adult fixed-dose formulations EVG/TAF/FTC and EVG/TDF/FTC have been studied in children, the latter one in children older than 12 years. This leaves little flexibility in adjusting doses for pediatric populations.

TAF in FDC Therapy

PK data for TAF in children have been reported simultaneously with data from EVG when the coformulated product was studied and is therefore included in this review. Just like TDF, TAF is a prodrug of tenofovir, but compared with TDF, TAF attains 90% lower circulating plasma concentrations of tenofovir.[123,124] Intracellular levels are however increased 2.4-fold when using TAF.[124] TAF has shown to be promising for use in children as, unlike TDF, it is not associated with side effects related to decreasing bone mineral density and renal tube defects.[125,126]

For treatment of HIV infection, TAF is currently available only in adult FDCs: FTC/TAF 200/25 mg, EVG/COBI/FTC/TAF 150/150/200/10 mg, and RIL/FTC/TAF 25/200/25 mg.

TAF is dosed 25 mg QD when used in FDCs without a booster (approved by the EMA and FDA in children ≥25 kg) and 10 mg QD when combined with a boosted PI or cobicistat (approved from 35 kg). The FDA has also approved using FTC/TAF 200/25 mg in combination with other ARV drugs (irrespective of the boosting effect of the third agent) in adults and adolescents ≥35 kg. With TAF, safety or efficacy is not related to plasma PK end points in adults or children.

In the 2 studies with TAF in children, safety and efficacy were comparable with adult data, although plasma AUC was 171% relative to adult AUC for children between 6 and 11 years old. Intracellular levels will need to be examined in children to relate dose to effect.

General Discussion and the Role of TDM

To the best of our knowledge, this is the first comprehensive review of the currently FDA- or EMA-approved and recommended pediatric ARV dosing and the evidence that informed these dosing recommendations. Current dosing recommendations for children are not always homogenous between international regulatory agencies and HIV management guidelines. Often, dosing of pediatric ART is based on small studies, and sometimes due to the location of the study among children from similar ethnic populations. Differences in metabolizing enzyme activity between ethnicities can result in differences in ARV PK in children. For instance, with the standard recommended dose, African children with lower CYP2B6 activity have an increased

chance of high EFV exposure, and Asian children are more likely to have high plasma ATV exposure because of the lower UGT enzymatic activity.[127]

PK models derived from small sample sizes of a heterogeneous population are essential to speedup drug investigation, approval, and use of novel ARVs, as they become available but carry the risk of covariate–parameter relationship misspecification, and subsequent extrapolation to other populations resulting in potential suboptimal doses.[128] A recently approved DTG dose for children below 40 kg and DRV/r QD dosing for children 6 to <12 years old are examples of modeled doses, which subsequently did not reach PK targets in PK studies. PK parameters in pediatric dosing studies have high variability, indicating uncertainty on how many children are exposed to inadequate drug levels. This highlights that postmarketing collection of TDM data, where feasible, could be helpful to validate model-based dosing strategies and inform dose adjustments where required.

In an effort to streamline the search for appropriate pediatric ART dosing and formulations, the WHO and UNITAID have recently developed the "Toolkit For Research And Development Of Pediatric Antiretroviral Drugs And Formulations," in which recommendations are made on how development of new pediatric ARV formulations and clinical trials in children can be made faster and more efficient.[10] Nevertheless, the development and approval of pediatric ARV formulations and pediatric dosing remains a lengthy process. To accelerate the development of pediatric formulations, efficacy should be extrapolated from adult trials provided the PK targets can be achieved, staggered age/weight-cohort enrollment design should be avoided, and adolescents should be enrolled in adult trials because all drug development studies in adolescents so far resulted in comparable plasma exposures, efficacy, and safety to adults.[10] Because weight-band dosing is now the preferred approach, this type of dosing should be studied upfront and included in the pediatric development plans with subsequent validation in clinical practice. The latter is particularly needed when a wide variation in PK is expected and the dose might not achieve target drug levels in all children.

It is important to know the grounds on which a dose is based to be able to evaluate the safety and to predict the efficacy of the used dosing without guidance of drug levels in the patient. TDM of ART is not recommended for routine clinical care. Moreover, even for resource-rich setting, the costs of implementing TDM to support clinical case management are high (ie, initial outlay for installation of analytical equipment and continued costs for maintenance), and often, there is a lack of expertise to interpret the results. Measuring plasma levels of ARVs also requires an acceptable turnaround time in order for the results to have a clinical impact. Such requirements might be problematic for facilities with limited resources and low numbers of patients in care. There are proposed drug concentration targets for certain ARVs (adult targets are summarized in Table 1), and when physicians are uncertain these targets are being achieved, TDM could be useful to guide clinical management. Such TDM data can then be used to monitor and validate clinical dosing, particularly when concomitant medication with known drug–drug interactions could be considered for drugs for which the dosing recommendations are based on insufficient data or little experience in practice. Moreover, these TDM data can be critical to evaluate recommended simplified dosing strategies proposed as part of a public health approach. In this context, innovative methods for TDM should also be explored to make TDM more affordable and accessible in LMIC. Methods such as dried blood spots could unlock TDM in countries where pediatric HIV is most prevalent.[129,130]

Currently, no commercial assay has been developed for the measurement of ARVs in plasma that has been approved by the EMA or FDA. TDM methods are therefore developed separately by each laboratory providing a TDM service for ARVs, usually based on assay descriptions published in the scientific literature. International interlaboratory quality control programs for measuring ARVs in plasma have been established to guard the proficiency of these analytical methods to be able to objectively validate the accuracy of TDM results and enable the comparison of results between labs.[131,132] When carried out using the right criteria, TDM is expected to improve individual patient outcomes and these data could be used to help increase our knowledge of the drug's effectiveness within the wider pediatric population. Therefore, TDM could be considered among the available tools to inform our global efforts to optimize dosing for children.

TABLE 1. Current Plasma Drug Targets for TDM of ARV Drugs

Drug	Plasma Target	Toxicity Considerations
NNRTI		
Efavirenz (EFV)	Mid-dose level ≥1 mg/L[29]	Mid-dose level <4 mg/L[30]
Nevirapine (NVP)	C_{trough} ≥3.0 mg/L[41]	No relation found between PK parameters and toxicity
Rilpivirine (RPV)	C_{trough} ≥0.042 mg/L[52,53]	C_{max}: <0.60 mg/L[52,53]
PIs		
Atazanavir (ATV)	C_{trough} ≥0.23 mg/L[55,56]	C_{trough}: 0.50–0.76 mg/L[58–60]
Darunavir (DRV)	C_{trough} ≥0.55 mg/L[73]	No relation found between PK parameters and toxicity
Lopinavir (LPV)	C_{trough} ≥1.0 mg/L[7,84]	No relation found between PK parameters and toxicity
InSTI		
Dolutegravir (DTG)	C_{trough} ≥0.324 mg/L[112]	No relation found between PK parameters and toxicity
Raltegravir (RTG)	C_{trough} ≥0.045 mg/L[115]	No relation found between PK parameters and toxicity
Elvitegravir (EVG)	C_{trough} ≥0.13[121]	No relation found between PK parameters and toxicity

Table 1 summarizes PK targets for the ARVs discussed in this review.

Limitations of this study are the inclusion of the literature written in English only and search with a single medical literature electronic database (PubMed), which could result in missing other PK data in children from studies not available on PubMed or not published in English.

CONCLUSION

This review summarizes the PK data available for ARVs in children. The information on which licensing and dosing guidelines are based is not as solid as might be perceived from viewing the drug labels or the dosing guidelines without a closer look at the studies from which the doses in the guidelines are drawn-up. Defining dosing in children is not without obstacles, and dosing of ARVs is actually more informed than many other types of drugs used in children. However, there are gaps in our current knowledge, which require further monitoring and PK studies in subpopulations, larger sample sizes where there is high interpatient variability in the PK parameters, and postmarketing real-life studies to confirm acceptability and safety. ARV concentration data generated from TDM can support our joint efforts to develop simplified safe and effective dosing of ARVs across the pediatric age continuum in the context of a public health approach.

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