CLINICAL

PHARMACOKINETICS OF ANTIRETROVIRAL DRUGS IN INFANCY

Helen McIlleron, *MB ChB, PhD*
Division of Clinical Pharmacology, Department of Medicine, University of Cape Town
Hermien Gous, *PharmD*
Harriet Shezi Children's Clinic, Enhancing Children's HIV Outcomes (ECHO), Chris Hani Baragwanath Hospital, Johannesburg

Dosing in infancy is complicated by inadequate characterisation of pharmacokinetics, unpredictable drug concentrations and a lack of suitable dosage forms. Additional challenges are presented by the concomitant administration of interacting drugs (e.g. rifampicin in antituberculosis treatment) and disease conditions that may alter drug disposition. The extent and implications of breastmilk transfer of drugs to the infant are poorly understood. New technologies facilitate pharmacokinetic studies in infants and will improve access to therapeutic drug monitoring.

Infancy (from birth until 1 year of age) is a time of rapid changes in the body of a child. These changes affect pharmacokinetics in many ways. The CHER study[1] showed that early antiretroviral (ARV) treatment reduces mortality and disease progression among infants acquiring HIV infection before 12 weeks of age. As a result the World Health Organization has recently revised treatment initiation recommendations in children less than 1 year of age: all infants under 12 months of age with confirmed HIV infection should be started on ARV therapy, irrespective of clinical or immunological stage.[2] Dosing in infants is challenging because drug concentrations are highly variable, there is frequently scant pharmacokinetic information on young children, and few suitable drug formulations are available. Furthermore, adherence to treatment is reliant on the caregiver rather than the patient. Peri- and postnatal HIV transmission are reduced by maternal highly active ARV treatment (HAART). However, the benefits and risks to breast-fed infants of exposure to maternal ARV drugs during lactation are poorly understood.

In this article we review the pharmacokinetics of ARV drugs relevant to South African infants, and highlight some of the challenges to delivering ARV treatment in safe and effective doses.

PHARMACOKINETIC PRINCIPLES

Growth and development are accompanied by changes that influence drug concentrations. As these developmental changes begin *in utero*, post-conceptional age is a better descriptor of maturation than postnatal age. Size and age explain a considerable part of the pharmacokinetic variability. However, there is a non-linear relationship between clearance and size. Consequently, simple proportional adjustment of the adult dose based on weight leads to underestimation of the maintenance dose required in children. Dose calculation methods based on scaling of clearance do not account for changes during early infancy in multiple processes affecting drug absorption, distribution, metabolism and elimination. In recent years there has been a trend to provide simplified dosing guidelines using weight bands, which provide many practical advantages. Ideally dosing would also account for differences in lean body size and maturity within the weight bands.

Drug absorption is highly variable and difficult to predict. It is determined by multiple interacting factors including enteric pH, gastric motility, intestinal transit time, the physico-chemical properties of the drug, intestinal metabolic capacity and activity of drug transporters. Gastric pH rapidly declines and then rises again during the first few days of life. Acidity then increases over several months, reaching adult levels (pH 2 - 3) between 2 and 7 years. Frequent feeding with milk or formula may influence gastric pH. The absorption of atazanavir is reduced at a higher pH and it should be taken with food to enhance bio-availability. Although by 36 weeks' gestational age an infant has developed intestinal motility patterns similar to those in adults, motility is irregular and variable, and the frequency of movement is reduced until 6 - 8 months of age. Dietary factors affect the rate of gastric emptying: increased caloric density feeds with increased concentrations of complex fat and sugars delay gastric emptying, so formula-fed infants may have shorter intestinal transit times than breast-fed infants.[3]

Body composition changes affect drug distribution. Total body water (TBW) comprises approximately 90% and 75% of body weight in preterm and term infants, respectively. By 1 year of age TBW approaches adult proportions of 60%. Extracellular fluid ranges from 65% in premature to 40% in term infants, while adult

values of 20% are reached after a year. Preterm infants have very little body fat (1 - 5%). Term infants typically have 12 - 15% body fat. By 12 months body fat increases to approximately 30% before declining to adult levels of 18%.

Tissue binding of drugs also affects their distribution. Bound drugs are inactive. Free drug concentration (unbound drug) gives a better indication of how much drug is available for distribution to the site of action. In adults, lopinavir is highly bound to plasma proteins (98 - 99%), mainly α_1-acid glycoprotein (AAG), for which it has the higher affinity, and albumin. Several other protease inhibitors (PIs) are highly bound to plasma proteins. Marked changes in plasma protein concentrations and their binding characteristics occur during the first 2 weeks after birth. Albumin, which binds acidic and neutral drugs, increases by almost 30% in the first week. Basic drugs bind to AAG, globulins and lipoproteins. Neonates have AAG concentrations one-third those of children aged 1 year and older. The lower pH of neonatal blood (7.25 - 7.3) results in an increased free fraction of some drugs. Moreover, drugs may compete with free fatty acids and unconjugated bilirubin for binding sites. The increased permeability of the blood-brain barrier during infancy may have implications for those with HIV-related encephalopathy.

PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) undergo extensive pre-systemic (in the intestine and liver) and systemic (largely hepatic) metabolism. The cytochrome P450 (CYP) enzymes CYP 3A4 (PIs and nevirapine) and CYP2B6 (NNRTIs) are important isoforms for ARV biotransformation. Unlike most nucleoside reverse transcriptase inhibitors (NRTIs), zidovudine and abacavir are extensively metabolised in the liver: both drugs by glucuronidation, and abacavir by the enzyme alcohol dehydrogenase. Maturation of drug metabolising enzymes accounts for age-associated differences in metabolism. Differential rates of maturation are associated with the specific metabolic enzymes. Activity of CYP 3A4 in the fetus is 30 - 70% of that in adults. CYP activity increases during infancy. By 1 year of age the activity of most CYP isoforms exceeds adult values. The capacity for glucuronidation is limited at birth and highly variable. Adult levels of activity are achieved between 2 months and 3 years of age.

The activity and expression of drug transporters such as p-glycoprotein are important determinants of drug absorption, distribution and clearance. Very little is known about the developmental pattern of these transporters which, like those of the drug metabolising enzymes, may be influenced by exogenous factors such as diet in addition to genetic and maturational determinants.

NRTIs other than zidovudine and abacavir are eliminated primarily unchanged by the kidneys. Both glomerular filtration and tubular secretion are immature at birth. Before 34 weeks' gestation the glomerular filtration rate (GFR) is reduced and highly variable. Thereafter, there is a strong correlation between GFR and age. Term infants have a GFR of 2 - 4 ml/min, which increases to 8 - 20 ml/min during the first few days of life. In contrast, premature infants may be born with a GFR of 0.6 - 0.8 ml/min, which may increase to 2 - 4 ml/min during the first few days after birth. By 3 - 6 months of age adult maturity in GFR is attained.[3]

There are frequently inadequate pharmacokinetic data on infants. Moreover, studies in infants are often limited by small sample size and sparse sampling. Table I sets out pharmacokinetic data for ARV drugs used in South African infants.

DOSAGE FORMS

Dosing of infants is challenging. They cannot swallow solid dosing forms. Liquid formulations often have decreased stability and require refrigeration. Stavudine, for example, comes in a powder that needs reconstitution before dispensing as an oral solution. It is stable for only 30 days in a refrigerator. Lopinavir/ritonavir solution may be stored at room temperature (up to 25°C) if it is used within 42 days. In many high-burden settings access to refrigeration is limited. Stability issues therefore complicate drug supply, storage and dispensing. Most tablets and capsules should not be crushed, as stability and absorption may be altered and accurate dosing is impossible. Dispensing and dosing errors are common, as the dose has to be translated into the volume dispensed or administered. Accurate measurement of the dose is challenging for many carers, and liquid formulations need to be shaken well before administration to ensure that the correct dose is administered. Relatively large-volume liquid doses can be problematic: infants do not always swallow the entire dose and often spit some of it out. Paediatric formulations such as dispersible fixed-dose combination tablets in doses suitable for infants and young children may provide considerable advantages.

THERAPEUTIC DRUG MONITORING

The routine use of therapeutic drug monitoring (TDM) has not been proven to alter treatment outcomes in adults. However, it is recommended that TDM be considered in paediatric patients (particularly infants and severely ill children) owing to unpredictable drug exposure and, in many instances, a paucity of evidence to support the dosing guidelines. Additional indications include potentially significant drug-drug (see 'Impact of antituberculosis treatment', below) or drug-food interactions; gastro-intestinal disease, or hepatic or renal

TABLE I. TARGET CONCENTRATIONS, AVERAGE CONCENTRATIONS IN ADULTS ON STANDARD ANTIRETROVIRAL DOSES AND PHARMACOKINETIC DATA FOR ANTIRETROVIRAL DRUGS USED IN SOUTH AFRICAN INFANTS

Drug (active ingredient/s)	Recommended dose in infants[11]	Recommended target concentration*	Average Pk in adult	Pk data in infants/ young children	Comments	References
Protease inhibitors						
Lopinavir (LPV)/ritonavir (co-formulated in a 4:1 ratio; Kaletra oral solution)	**14 days - 6 months:** 300 mg LPV/ m2 BSA 12-hourly, or 16 mg LPV/kg 12-hourly >6 months: 230 mg LPV/m^2, 12 mg LPV/kg if <15 kg, or 10 mg LPV/kg if ≥15 kg. Doses given 12-hourly	Lopinavir C_{min} >1.0 mg/l	C_{min} 5 - 8 mg/l	**<8 weeks:** Median LPV C_{min} 2.22 mg/l (9 infants aged 5.6 - 7.9 weeks; median dose 276 mg/m^2) **6 weeks - 6 months:** C_{min} 2.37 mg/l (18 infants 1.6 - 5.9 months old; average dose 267 mg/m^2). In both studies PK sampling was 2 weeks after starting treatment. As C_{min} increased at later times, difficulties with dose administration may in part account for low concentrations **>6 months:** Median C_{min} 4.64 mg/l (15 South African children 9 - 47 months; median LPV dose 269 mg/m^2)	Once-daily dosing is NOT recommended. No data in combination with anti-TB treatment, NNRTIs or other PIs in <6-month-olds. AUC in children >6 months dosed with 230 mg LPV/m^2 approximates that in adults, although C_{min} is lower	4 - 6
Ritonavir (RTV)	**> 1month:** 350 - 450 mg/m^2 BSA 12-hourly	C_{min} >2.1 mg/l	C_{min} 4 mg/l	4 weeks - 24 months: C_{min} was low and highly variable among 35 infants: RTV 350 mg/m^2 twice daily and 450 mg/m^2 twice daily resulted in median C_{min} of 0.99 mg/l and 0.74 mg/l, respectively	Not recommended in infants ≤1 month old; doses of 450 mg/m^2 12-hourly resulted in low plasma concentrations. Low RTV concentrations are linked to inferior viral responses in children	7, 8
Indinavir (IDV)	Not approved for use in children	C_{min} >0.1 mg/l C_{max} <10.0 mg/l	IDV alone: C_{min} 0.1 - 0.4 mg/l; IDV/r: C_{min} 0.2 - 0.5 mg/l	3 month- to 16-year-olds given IDV 50 mg/kg (±600 mg/m^2) 8-hourly achieved C_{min} median (range) 0.07 mg/l (0.02 - 0.21). CL/F was higher in <6-year-olds (2.5 v. 1.0 l/h/kg) and more variable. IDV 400 mg/m^2 plus 100 - 125 mg/m^2 ritonavir 12-hourly achieves satisfactory IDV concentrations in older children	Should not be used in neonates owing to the risk of kernicterus. A safe and effective dose has not been established in children. Dose-related nephrolithiasis is a concern	9 - 11

TABLE I. CONTINUED

Drug (active ingredient/s)	Recommended dose in infants[11]	Recommended target concentration*	Average Pk in adult	Pk data in infants/ young children	Comments	References
Protease inhibitors						
Nelfinavir (NFV)	Not approved for use in <2-year-olds	C_{min} >0.8 mg/l	C_{min} 1.5 mg/l	NFV 45 mg/kg twice daily from birth: median C_{min} 3.2 mg/l on day 7, but by day 14 and 28 only 0.7 mg/l. Similarly, <6-week-olds on 40 mg/kg twice daily achieved median C_{min} 1.35 mg/l with 3 of 11 infants failing to reach AUC targets. Older infants may require even higher doses: 50% of 2.3 - 8.5-month-olds on an average 136 mg NFV/kg/d failed to reach the AUC target	Doses of NFV 25 - 35 mg/kg 3 times a day, or 45 - 55 mg/kg twice daily, are used in children 2 - 13 years, but younger children require higher doses	12 - 14
Atazanavir (ATV)	Not approved for use in children <6 years of age	C_{min} >0.15 mg/l	ATZ 400 mg/d: C_{min} 0.27 mg/l; ATZ/RTV 300/100 mg/d: C_{min} 0.86 mg/l	The recently reported results of NIH PACTG study P1020A demonstrated adequate ATV concentrations (C_{min} 0.43 mg/l; AUC_{0-24} 48.54 mg/h/l) in 3 - 24-month-olds using RTV boosted ATV 339 mg/m². CL/F was high in infants (12.4 l/h/m^2 with median age 0.8 years v. 2.9 l/h/m^2 with median age 10.5 years)	Avoid in <3-month-olds: risk of kernicterus. RTV-boosting achieves higher C_{min} with lower C_{max}, and inter-individual variability is reduced. Higher mg/m^2 doses are required in children compared with adults: the recommended daily dose in infants >3 months old is ATV/RTV 310/100 mg/m^2	15,16
Non-nucleoside reverse transcriptase inhibitors						
Nevirapine (NVP) for PMTCT	**Perinatal:** 200 mg single maternal dose during labour + single dose of 2 mg/kg to infant up to 72 h after birth	C_{min} >0.1 mg/l (10 × *in vitro* IC_{50})	-	Transplacental transfer after a single maternal 200 mg dose during labour maintains infant NVP >0.1 mg/l for several days. A 2 mg/kg NVP dose at 48 - 72 h keeps NVP >0.1 mg/l for a week in most infants (0.11 - 0.28 mg/l in 7-day-old infants). A study evaluating chronic NVP (4 mg/kg from birth to 14 days, then 8 mg/kg until 24 weeks) for breast-feeding infants found NVP >0.1 mg/l in 95% and 100% of those receiving twice weekly or daily doses; once-weekly dosing was insufficient in >60% of infants	Evaluation of chronic NVP administration (4 mg/kg/d) for prevention of breastmilk transmission is ongoing. Long-term maternal NVP before delivery accelerates NVP elimination in newborns, presumably due to *in utero* autoinduction of NVP elimination	17 - 19

TABLE I. CONTINUED

Drug (active ingredient/s)	Recommended dose in infants[11]	Recommended target concentration*	Average Pk in adult	Pk data in infants/ young children	Comments	References
Non-nucleoside reverse transcriptase inhibitors						
Nevirapine	**>14 days:** 150 - 200 mg/m^2 BSA once daily for 14 days then twice daily	C_{min} >3.0 mg/l	C_{min} 4 - 6 mg/l	Zambian infants (mean age 5.3 months) had mean NVP AUC_{0-12h}, C_{max} and C_{min} of 78.7 h/mg/l, 8.1 mg/l, and 4.9 mg/l, respectively. Three of 6 infants <5 months old (receiving NVP 324 - 406 mg/m^2/day, in 2 doses), had subtherapeutic C_{min}	NVP absorption is variable and delayed. Elimination is prolonged in newborns, but accelerates during the first days of life; infants require higher mg/m^2 doses than older children	20
Nucleoside reverse transcriptase inhibitors						
Lamivudine	**<30 days:** 2 mg/kg twice a day **≥30 days:** 4 mg/kg twice daily	-	CL/F 0.3 l/h/kg; $t_{1/2}$ 6 h; IC $t_{1/2}$ (of active triphosphate) 15 h	**Infants 3 - 28 days old:** mean CL/F 0.37 l/h/kg; AUC_{0-12} 6.0 mg/h/l on 2 mg/kg twice daily. In contrast, infants >1 month had mean CL/F 0.66 l/h/kg; 4 mg/kg twice daily achieved mean AUC 6.8 mg/h/l	Excreted unchanged in the urine. CL/F doubles during the first month, after which it stabilises for the duration of infancy	21
Zidovudine (ZDV) for PMTCT and premature infants	**<2 weeks:** 2 mg/kg/12 h (IV: 1.5 mg/kg) **2 - 6 weeks:** increase to 8-hourly			CL/F is low in premature neonates (0.15 l/h/kg). In term newborns CL/F is 0.34 l/h/kg before increasing rapidly to 0.65 l/h/kg by 7 days and 1.14 l/h/kg in infants >14 days old		22
Zidovudine	**<6 weeks:** 2 mg/kg/6 h (IV: 1.5 mg/kg) **≥6 weeks:** 4 - <9 kg: 12 mg/kg/12 h; **≥9 kg:** 9 mg/kg/12 h	-	CL/F 1.5 l/h/kg; $t_{1/2}$ 1.1 h		1st-pass metabolism reduces bioavailability by 35%. Undergoes hepatic glucuronidation; a small amount is excreted unchanged in urine	
Stavudine	**0 - 13 days:** 0.5 mg/kg 12-hourly **>13 days:** 1 mg/kg 12-hourly	-	CL/F 35.6 l/h; $t_{1/2}$ 1 h; IC $t_{1/2}$ 3.5 - 7.0 h	CL/F 5.6 ml/min/kg at 1 week, 6.8 ml/min/kg at 6 weeks. On 1 mg/kg/12 h, 14- and 28-day-olds had similar AUC (1.9 mg/h/l) and $t_{1/2}$ (1.1 - 1.2 h)	Absorption is delayed in neonates	23
Didanosine	**2 weeks - 8 months:** 100 mg/m^2 12-hourly **>8 months:** 120 mg/m^2 12-hourly	-	CL/F 1 l/h/kg; $t_{1/2}$ 1.5 h; IC $t_{1/2}$ 12 - 40 h	Although variable, one study found little change in CL/F between the 1st day of life and 6 weeks (CL/F 4.5 and 5.0 l/min/m^2 respectively). Other sources report CL/F to be 4-fold higher in 6-week-olds than in newborns	50 mg/m^2 12-hourly is recommended in newborns. Unstable at low pH (hence given with antacid)	23

TABLE I. CONTINUED

Drug (active ingredient/s)	Recommended dose in infants[11]	Recommended target concentration*	Average Pk in adult	Pk data in infants/ young children	Comments	References
Non-nucleoside reverse transcriptase inhibitors						
Abacavir	**≥3 months:** 8 mg/kg twice daily	-	300 mg^2 × day and 600 mg daily: AUC_{0-24} 8 mg/h/l	Single 8 mg/kg dose in 3 - 23-month-olds: mean AUC 8.67 mg/h/l. There are few data in infants receiving repeated doses, but the drug's pharmacokinetic properties are similar across age groups	Not approved for use in <3-month-olds. Clearance is increased in children; the recommended 8 mg/kg dose is double the adult mg/kg dose	24

*Concentration-based cut-off values for performing TDM of antiretroviral agents in naïve patients.[25]
Pk = pharmacokinetic; PMTCT = prevention of mother-to-child transmission; BSA = body surface area; IV = intravenous; IC = intracellular; AUC = area under the concentration-time curve; CL/F = apparent clearance; C_{max} = peak concentration; C_{min} = trough/minimum concentration; IC_{50} = 50% inhibitory concentration; $t_{1/2}$ = half life.
Fosamprenavir is not approved for use in infants but is currently being evaluated in South African children 1 - 6 months old.

impairment; treatment-experienced patients who may have viral isolates with reduced susceptibility to highly active ARV therapy (HAART); use of alternative dosing regimens the safety and efficacy of which have not been established in clinical trials; concentration-dependent toxicity; unexpectedly poor virological response in a treatment-naïve person; and monitoring of adherence.[25]

The minimum (predose trough) drug concentration is used to monitor virological efficacy. Peak concentrations relate more closely to toxicity for some drugs, and the area under the drug concentration-time curve is a measure of overall systemic exposure. Therapeutic ranges have not been defined for NRTIs, which are metabolised intracellularly to the active triphosphate, as plasma concentrations are not closely related to efficacy.

Target concentrations for NNRTIs and PIs (Table I) are based largely on studies in adults. While it is likely that good responses to treatment will be achieved in children, provided that they are given drug formulations and doses that achieve drug exposure similar to those that have demonstrated safety and efficacy among adults, important differences may apply. Routinely, total plasma ARV concentrations are measured in the laboratory. The recommended drug concentration ranges are therefore based on the sum of the free active component and protein-bound drug. Altered protein binding during early infancy may alter the proportion of active drug in the measured concentration. Furthermore, day-to-day variability complicates interpretation of a single drug concentration result. Drug concentration results should be interpreted on an individual basis, and safety and efficacy should also be carefully monitored. Clearly, poor adherence to treatment needs to be ruled out as a cause of low drug concentrations before dose adjustments are made.

Modern technologies such as liquid chromatography mass spectrometry allow drug concentration measurement in low-volume samples, thus facilitating TDM in infants. The development of methods using blood spots dried onto filter paper is likely to make TDM increasingly accessible and affordable. However, although it is frequently indicated in infants as part of an integrated approach, TDM of ARVs is currently not available to the vast majority patients in high-burden settings.

IMPACT OF ANTITUBERCULOSIS TREATMENT

Although the use of ARV therapy complicates the management of tuberculosis, patients with tuberculosis who meet the criteria for ARV therapy should be started on an effective ARV regimen once they are established on rifampicin-based antituberculosis treatment.

Through activation of the pregnane X receptor, which results in increased expression of multiple drug metabolising enzymes and transporters, rifampicin increases the oral clearance of many medications. Rifampicin lowers the concentrations of PIs to subtherapeutic levels; nevirapine trough concentrations are reduced by about 30% in South African adults;[26] and zidovudine concentrations are reported to decline by 50%. There are concerns associated with all the currently available co-treatment options for infants, and there are very few data on which to base optimal co-treatment approaches. Careful monitoring is indicated.

In HIV-infected infants exposed to single-dose nevirapine, or maternal NNRTI-containing ARV treatment or prevention regimens, PI-based HAART should be started. Super-boosted lopinavir (extra ritonavir is added to lopinavir/ritonavir; a total 12-hourly lopinavir/ritonavir dose of 230/230 mg/m^2) achieves adequate lopinavir exposure in most children older than 6 months during rifampicin-containing antituberculosis treatment.[27] However, lopinavir concentrations are highly variable, there are no data to support this approach in younger infants, and it is poorly tolerated and complex to prescribe, dispense and administer. Double-dose lopinavir/ritonavir has been shown to result in sub-therapeutic concentrations in children during antituberculosis treatment. When adjusted doses of PIs are used with rifampicin, TDM should be implemented if it is available, and it is essential to regularly monitor liver function. Rifabutin (in reduced doses) is preferred to rifampicin in adults requiring PIs, but it is expensive and suitable formulations are not available for infants and young children.

In many settings nevirapine plus 2 NRTIs is the only effective treatment option available to young children. Standard doses of nevirapine twice daily provide acceptable outcomes in adults with tuberculosis (although it is inferior to efavirenz). Recent evidence suggests, however, that the majority of young children on tuberculosis treatment fail to achieve trough concentrations >3 mg/l (the lower limit of the recommended range),[28] and data for infants younger than 6 months are lacking. The approach should be used with caution until more safety and efficacy information is available, and patients should be carefully monitored.

ARV regimens comprising 3 or 4 nucleos(t)ides have inferior efficacy compared with PI- and NNRTI-based regimens, and are not adequately evaluated in children. However, they may have a role in ARV-naïve patients with HIV-associated tuberculosis, as the substantial interactions of rifampicin with the PIs and NNRTIs are avoided.

ARVS IN BREASTMILK

The use of ARV drugs by mothers is increasing as access to treatment programmes improves, thresholds for starting treatment become less stringent and ARVs are implemented to prevent HIV transmission during childbirth and breastfeeding. However, the benefits and risks to breastfed infants of exposure to maternal ARV drugs during lactation are poorly understood. The different physicochemical properties of drugs lead to differential transfer from maternal plasma to breastmilk (Table II) and to the breastfed infant. Incomplete exposure of infants to components of a maternal regimen may favour the selection of drug-resistant virus should transmission occur. Little is known about the safety of ARVs in breastmilk. The small doses of NRTIs and PIs ingested through breastmilk may invoke subtle or idiosyncratic side-effects, while the more substantial exposure to nevirapine and efavirenz are of more importance.

A study of ARV concentrations in exclusively breastfed Kenyan infants younger than 6 months, whose mothers were receiving HAART, found biologically significant concentrations of lamivudine and nevirapine, but not zidovudine.[29] Lamivudine concentrations were just greater than the 50% inhibitory concentration (IC_{50}) for wild-type HIV. Median nevirapine concentrations (0.90 mg/l) were well above the median HIV IC_{50} (0.017 mg/l).[29] Rwandan infants of mothers receiving efavirenz-based HAART achieved median efavirenz concentrations of 0.87 mg/l through breastmilk ingestion, just below the recommended target trough concentration of >1 mg/l.[30] Transfer of NNRTIs from mothers receiving HAART may therefore result in substantial exposure in their breastfed infants along with potential benefit for prevention of HIV transmission, the risk of side-effects and the risk of developing viral resistance to NNRTIs

TABLE II. ANTIRETROVIRAL DISTRIBUTION TO BREASTMILK AND INFANT EXPOSURE RESULTING FROM MATERNAL HAART

Drug	Median breastmilk/maternal plasma ratio (IQR)	Estimated median daily infant dose from breastmilk	Median infant concentration	Reference
Zidovudine	0.44 (0.23, 0.65)	1.35 µg/kg/d (<1 000 × lower than standard infant dose for PMTCT)	Undetectable*	29
Lamivudine	2.56 (1.79, 3.89)	182 µg/kg (2% daily treatment dose for >3-month-olds)	0.02 - 0.03 mg/l*	29
Nevirapine	0.75 (0.64, 0.89)	600 µg/kg/d (15% of the 4 mg/kg/d infant dose being evaluated in PMTCT studies)	0.73 - 1.03 mg/l*	29
Efavirenz	0.52 (0.43, 0.62)	-	0.87 mg/l†	30
Lopinavir	0.11 (0.06, 0.15)	-	Undetectable†	31
Ritonavir	0.11 (0.08, 0.18)	-	Undetectable†	31

*Whole blood concentrations from 2 to 14 weeks after birth.
†Plasma concentrations 6 weeks to 6 months after birth.
IQR = intraquartile range; PMTCT = prevention of mother-to-child transmission.

should HIV transmission occur. Conversely, breastmilk concentrations of PIs are low and there is little if any transfer to the infant via breastmilk.[31]

CONCLUSION

The pharmacokinetics of infancy are unique and evolve rapidly during this period of life. Drug doses used during infancy are often based on extrapolation from other age groups. For many of the ARV drugs, evidence to support the dosing approaches is rudimentary and suitable dosage forms are lacking. It is important to ensure that adequate concentrations of ARV drugs are obtained, to ensure efficacy and prevent toxicity. The infant is further exposed to maternal ARV drugs before and during birth, and during lactation. There is an urgent need for pharmacokinetic studies in the relevant infant populations to support optimal dosing approaches which should then undergo more extensive evaluation of efficacy and safety. As drug concentrations in infants are highly unpredictable, particularly in neonates and premature infants, severely ill children or those treated concomitantly with interacting medications, TDM has a role in optimising individual dosing.

Acknowledgement

HM received research support from the European and Developing Countries Clinical Trials Partnership. HG received support from ECHO, IMPAACT and PEPFAR.

REFERENCES

1. Violari A, Cotton MF, Gibb DM, *et al.* Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med* 2008; 359: 2233-2244.
2. World Health Organization. Report of the WHO Technical Reference Group, Paediatric HIV/ART Care Guideline Group Meeting, WHO Headquarters, Geneva, Switzerland, 10-11 April 2008. www.who.int/hiv/pub/paediatric/WHO_Paediatric_ART_guideline_rev_mreport_2008.pdf (accessed 6 June 2009).
3. Maples HD, James LP, Stowe CD. Special pharmacokinetic and pharmacodynamic considerations in children. In: Burton ME, Shaw LM, Schentag JJ, Evans WE, eds. *Applied Pharmacokinetics & Pharmacodynamics.* 4th ed. Baltimore: Lippincott Williams & Wilkins, 2006: 213-230.
4. Chadwick EG, Pinto J, Yogev R, *et al.* Early initiation of lopinavir/ritonavir in infants less than 6 weeks of age: pharmacokinetics and 24-week safety and efficacy. *Pediatr Infect Dis J* 2009; 28: 215-219.
5. Chadwick EG, Capparelli EV, Yogev R, *et al.* Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age: 24 week results. *AIDS* 2008; 22: 249-255.
6. Ren Y, Nuttall JJ, Egbers C, *et al.* Effect of rifampicin on lopinavir pharmacokinetics in HIV-infected children with tuberculosis. *J Acquir Immune Defic Syndr* 2008; 47: 566-569.
7. Chadwick EG, Rodman JH, Britto P, *et al.* Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J.* 2005; 24: 793-800.
8. Dumon C, Solas C, Thuret I, *et al.* Relationship between efficacy, tolerance, and plasma drug concentration of ritonavir in children with advanced HIV infection. *Ther Drug Monit* 2000; 22: 402-408.
9. Burger DM, van Rossum AM, Hugen PW, *et al.* Pharmacokinetics of the protease inhibitor indinavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother* 2001; 45: 701-705.
10. Bergshoeff AS, Fraaij PL, van Rossum AM, *et al.* Pharmacokinetics of indinavir combined with low-dose ritonavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother* 2004; 48: 1904-1907.
11. Curras V, Hocht C, Mangano A, *et al.* Pharmacokinetic study of the variability of indinavir drug levels when boosted with ritonavir in HIV-infected children. *Pharmacology* 2009; 83: 59-66.
12. Rongkavilit C, van Heeswijk RP, Limpongsanurak S, *et al.* Dose-escalating study of the safety and pharmacokinetics of nelfinavir in HIV-exposed neonates. *J Acquir Immune Defic Syndr* 2002; 29: 455-463.
13. Mirochnick M, Stek A, Acevedo M, *et al.* Safety and pharmacokinetics of nelfinavir coadministered with zidovudine and lamivudine in infants during the first 6 weeks of life. *J Acquir Immune Defic Syndr* 2005; 39: 189-194.
14. Litalien C, Faye A, Compagnucci A, Giaquinto C, *et al.* Pharmacokinetics of nelfinavir and its active metabolite, hydroxy-tert-butylamide, in infants perinatally infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J* 2003; 22:48-55.
15. Rutstein R, Samson P, Kiser J, *et al.* The PACTG 1020A Protocol: Atazanavir with or without ritonavir in HIV-infected infants, children, and adolescents. Presented at the 14th Conference on Retroviruses and Opportunistic Infections, 25 - 28 February 2007, Los Angeles (Abstract 715).
16. Kiser J, Rutstein R, Aldrovandi G, *et al.* Pharmacokinetics of atazanavir/ritonavir in HIV-infected infants, children, and adolescents: PACTG 1020A. Presented at the 12th Conference on Retroviruses and Opportunistic infections, 22 - 25 February 2005, Boston (Abstract 767).
17. Mirochnick M, Fenton T, Gagnier P, *et al.* Pharmacokinetics of nevirapine in human immunodeficiency virus type 1-infected pregnant women and their neonates. Pediatric AIDS Clinical Trials Group Protocol 250 Team. *J Infect Dis* 1998; 178: 368-374.
18. Shetty AK, Coovadia HM, Mirochnick MM, *et al.* Safety and trough concentrations of nevirapine prophylaxis given daily, twice weekly, or weekly in breast-feeding infants from birth to 6 months. *J Acquir Immune Defic Syndr* 2003; 34: 482-490.
19. Six Week Extended-Dose Nevirapine (SWEN) Study Team, Bedri A, Gudetta B, *et al.* Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *Lancet* 2008; 372: 300-313.
20. Mulenga V, Fillekes Q, Kabamba D, *et al.* Pharmacokinetics of nevirapine in 3- to 6-kg, HIV-infected infants taking pediatric fixed-dose combination tablets. Presented at the 16th Conference on Retroviruses and Opportunistic infections, 8 - 11 February 2007, Montreal (Abstract 881).
21. Tremoulet AH, Capparelli EV, Patel P, *et al.* Population pharmacokinetics of lamivudine in human immunodeficiency virus-exposed and -infected infants. *Antimicrob Agents Chemother* 2007; 51: 4297-4302.
22. Pacifici GM. Pharmacokinetics of antivirals in neonate. *Early Hum Dev* 2005; 81:773-780.
23. Capparelli E, Rakhmanina N, Mirochnick M. Pharmacotherapy of perinatal HIV. *Semin Fetal Neonatal Med* 2005; 10: 161-175.
24. Yuen GJ, Weller S, Pakes GE. A review of the pharmacokinetics of abacavir. *Clin Pharmacokinet* 2008; 47: 351-371.
25. La Porte CJL, Back DJ, Blaschke T, *et al.* Updated guideline to perform therapeutic drug monitoring for antiretroviral agents. *Reviews in Antiviral Therapy* 2006; 3: 4-14.
26. Cohen K, Van Cutsem G, Boulle A, *et al.* Effect of rifampicin-based antitubercular therapy on nevirapine plasma concentrations in South African adults with HIV-associated tuberculosis. *J Antimicrob Chemother* 2008; 61(2): 389-393.
27. Ren Y, Nuttall JJ, Egbers C, *et al.* Effect of rifampicin on lopinavir pharmacokinetics in HIV-infected children with tuberculosis. *J Acquir Immune Defic Syndr* 2008; 47(5): 566-569.
28. Oudijk M, McIlleron H, Mulenga H, *et al.* Pharmacokinetics of nevirapine in young children during combined ART and rifampicin-containing antituberculosis treatment. Presented at the IAS Conference, 19 - 22 July 2009, Cape Town. (Abstract LBPEB10).
29. Mirochnick M, Thomas T, Capparelli E, *et al.* Antiretroviral concentrations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. *Antimicrob Agents Chemother* 2009; 53: 1170-1176.
30. Schneider S, Peltier A, Gras A, *et al.* Efavirenz in human breast milk, mothers', and newborns' plasma. *J Acquir Immune Defic Syndr* 2008; 48: 450-454.
31. Corbett A, Martinson F, Rezk N. Lopinavir/ritonavir concentrations in breast milk and breast-feeding infants. Presented at the 16th Conference on Retroviruses and Opportunistic Infections, 8-11 February 2009, Montreal (Abstract 947).
32. Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. 23 February 2009, pp. 1-139. http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf (accessed 30 June 2009).