PAEDIATRIC ANTIRETROVIRAL PHARMACOLOGY

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HIV is a rapidly fatal disease in resource-poor environments where access to antiretroviral (ARV) therapy is limited. Despite the increasing availability of ARV therapy, the epidemic continues to grow especially among women of child-bearing age and children. The appropriate use of ARVs requires careful consideration of each drug's disposition kinetics, as well as the impact on the agent of pharmacokinetic and pharmacodynamic developmental changes occurring across the paediatric age continuum. Drug absorption may be altered by limited gastric acid and lipase secretion in infants. Dietary differences and feeding patterns may also affect drug absorption. Lower plasma protein levels and higher body water content in infants can modify drug disposition. Altered elimination of ARVs is seen both for renal and hepatic routes of drug removal. While reduced in infants, renal and hepatic drug elimination increase over the first 2 years of life, attaining more rapid elimination than in adults. However, the precise pattern of maturation varies among the metabolic enzymes responsible for ARV biotransformation. In addition to these pharmacokinetic differences, formulation limitations impact on delivery of ARV therapy in the paediatric population. Liquid forms are not available for many ARVs, and when they are available they may require refrigeration, lack stability data in hot climates or require large storage areas. Even for solid oral dosage forms, the breaking, crushing and mixing of adult formulations with food or liquids to administer ARVs to children may affect their bioavailability.

Altered ARV disposition is most pronounced in infancy. Given the success of antepartum, peripartum and postnatal ARVs to limit mother-to-child transmission (MTCT), these drugs are being used in a large number of newborns. Smaller doses of zidovudine, lamivudine and nevirapine (NVP) have been used to take into account the reduced elimination. In general these have been well tolerated in infants. HIV resistance following single-dose NVP therapy may be the result of its long half-life and raises concerns regarding future therapy options in both the mother and infant. Tenofovir is currently being investigated as a potential alternative short-course agent for prevention of MTCT. Infants may also receive meaningful ARV exposure as a result of depressed elimination capacity and via ingestion of breastmilk from mothers receiving therapy.

Editor's note: This is an excellent article. However, the dosages mentioned are based on American guidelines and package inserts. African readers are advised to consult the two guidelines in this journal, as dosages may differ.

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

NRTIs are synthetic analogues of naturally occurring nucleosides used by cells for DNA replication. These agents preferentially target the HIV-1 reverse transcriptase enzyme, which is responsible for transcribing viral RNA into viral DNA for eventual integration into the host's cellular DNA. For activity, nucleosides require intracellular phosphorylation into the active nucleotide moiety. It is the *intracellular* rather than serum concentrations of these agents that more closely reflect their antiviral potency. Longer intracellular half-lives of some nucleosides allow for once-daily dosing and easier adherence. Some adverse effects of NRTIs are probably caused by impairing DNA replication, affecting mitochondrial function. The stavudine and didanosine combination should be avoided because maternal deaths have occurred from lactic acidosis and/or hepatotoxicity (Table I).

In general, the NRTIs share similar pharmacokinetics (Table II). In general, these agents have good bioavailability and can be given without regard to food. Didanosine, which is acid labile and co-formulated with antacids, is the exception with low bioavailability that is improved when given without food. The NRTIs have limited protein binding and distribute widely into tissues, including the placenta, cerebrospinal fluid, and breastmilk. None undergo extensive liver metabolism via the cytochrome P450 system (CYP450) and all are either renally eliminated or metabolised by other hepatic enzymes. Therefore, drug interactions via the CYP450 system do not occur with NRTIs, although other pharmacokinetic interactions do occur (e.g. higher didanosine concentrations with tenofovir). Zidovudine, didanosine, stavudine, lamivudine and abacavir exhibit very rapid elimination from plasma. All are available in liquid formulations.

ZIDOVUDINE

Zidovudine is a thymidine analogue and was the first ARV agent. Following absorption, zidovudine undergoes

TABLE I. AVAILABLE ANTIRETROVIRAL THERAPEUTIC AGENTS*

Drug	Dose	Major toxicities	Other comments
Nucleoside/tide reverse transcriptase inhibitors			
Abacavir (ABC, Ziagen) 300 mg tab 20 mg/ml sol	**< 3 mo.:** 8 mg/kg bid is under investigation **> 3 mo.:** 8 mg/kg (max 300 mg) bid **Adolescents:** 300 mg bid	Nausea, vomiting, fever, headache, diarrhoea, rash, anorexia, lactic acidosis, hepatic steatosis, hypersensitivity reaction (in 2 - 5% can be FATAL), pancreatitis, hepatitis, fatigue, hypertriglyceridaemia	Syrup is well tolerated or tablet may be crushed Can be given with food WARN PARENTS ABOUT HYPERSENSITIVITY REACTION Discontinue ABC permanently and never rechallenge if hypersensitivity reaction occurs
Didanosine, dideoxyinosine (ddI, Videx) 25, 50, 100, 150, 200 mg chew tab 100, 167, 250 mg pwdr pkt 10 mg/ml susp 125, 200, 250, 400 mg EC tab	**< 90 d:** 50 mg/m^2 12-hrly **> 90 d:** 120 (range 90 - 150) mg/m^2 12-hrly **Adolescents:** < 60 kg: 125 mg bid OR 250 mg qd (EC form) > 60 kg: 200 mg bid OR 400 mg qd (EC form)	GI disturbances, peripheral neuropathy, electrolyte disturbances, hyperuricaemia, lactic acidosis, hepatic steatosis, pancreatitis, diarrhoea, retinal depigmentation	Suspension must be refrigerated; stable for 30 days; shake well before use Administer dose 1 h before or 2 h after food; may be less important in children Enteric-coated beadlets in capsules may be opened and sprinkled on small amount of food
Lamivudine (3TC, Epivir) 150, 300 mg tab 10 mg/ml sol	**< 30 d:** 2 mg/kg bid† **≥ 30 d:** 4 mg/kg bid† **Adolescents:** < 50 kg: 2 mg/kg > 50 kg: 150 mg bid OR 300 mg qd †not FDA approved under 3 mo.	Headache, fatigue, GI disturbances, pain, pancreatitis, peripheral neuropathy, neutropenia, hepatitis, hepatic steatosis, lactic acidosis	Can be given with food Well tolerated Store solution at room temperature and use within 1 month of opening
Stavudine (d4T, Zerit, Zerit XR) 15, 20, 30, 40 mg cap 75, 100 mg XR cap 1 mg/ml sol	**≤ 6 mo.:** Under evaluation (PACTG protocol 332) **≥ 6 mo.:** 1 mg/kg 12-hrly up to 30 mg **Adolescents:** 30 - 60 kg: 30 mg bid or 75 mg XR qd > 60 kg: 40 mg bid or 100 mg XR bid	Headache, GI disturbances, rash, peripheral neuropathy, pancreatitis, lactic acidosis, hepatic steatosis	Large volume of solution Refrigerate solution; stable for 30 days Store in glass bottles Shake well before administration Capsules may be opened and mixed with small amount of food; stable in solution for 24 h if refrigerated Do not use with AZT (antagonistic)
Tenofovir disoproxil fumarate (TDF, Viread) 300 mg tab	No neonatal or paediatric data, but phase I study in children ≥ 4 yrs currently enrolling (NCI protocol 020006) **≥ 18 yrs:** 300 mg qd	GI disturbances, lactic acidosis, hepatic steatosis, bone and renal toxicity in animals, not seen in adult humans but experience limited	Tablet can be crushed and mixed in water or juice
Zidovudine (AZT, ZDV, Retrovir) 300 mg tab 100 mg cap 10 mg/ml syrup 10 mg/ml injectable	**Premature infants < 34 wks gestational age:** 1.5 mg/kg IV 12-hrly or 2 mg/kg PO 12-hrly, increased to 8-hrly at 2 wks post-conceptional age if ≥ 30 wks or at 4 wks post-conceptional age if < 30 wks gestational age **Term infants < 90 d:** 2 mg/kg PO 6-hrly or 1.5 mg/kg IV 6-hrly **≥ 90 d:** 160 mg/m^2 8-hrly (range 90 - 180 6 - 8-hrly) or 120 mg/m^2 IV 6-hrly or 20 mg/m^2/h continuous IV Some experts recommend 180 mg/m^2 12-hrly when used in combination with other ARV drugs, but data are limited **Adolescents:** 200 mg tid or 300 mg bid	Anaemia, neutropenia, headache, myopathy, myositis, hepatitis, lactic acidosis, hepatomegaly and hepatic steatosis	Large volume of syrup not well tolerated in older children Requires storage in glass jars; light-sensitive Can be given with food Do not use with d4T (antagonistic)

TABLE I. AVAILABLE ANTIRETROVIRAL THERAPEUTIC AGENTS* (CONTINUED)

Drug	Dose	Major toxicities	Other comments
Non-nucleoside reverse transcriptase inhibitors			
Efavirenz (EFV, Sustiva) 50, 100, 200 mg cap 600 mg tab	**10 - < 15 kg:** 200 mg at night (not FDA approved under 3 yrs) **15 - < 20 kg:** 250 mg at night **20 - < 25 kg:** 300 mg at night **25 - < 32.5 kg:** 350 mg at night **32.5 - < 40 kg:** 400 mg at night **> 40 kg:** 600 mg at night	Dizziness, dream and sleep disturbances, agitation, feeling 'disconnected', amnesia, impaired concentration, hallucinations, rash, teratogenesis in primates (avoid in pregnancy)	Capsules may be opened and added to food, but have a peppery taste that can be disguised when mixed with sweet foods or jam Can be given with food, but avoid high-fat meals Administer at bedtime preferably to reduce central nervous system side-effects especially in the first 2 weeks Drug interactions
Nevirapine (NVP, Viramune) 10 mg/ml susp 200 mg tab	**≤ 2 mo.:** 5 mg/kg or 120 mg/m^2 qd x 14 d, then 120 mg/m^2 12-hrly x 14 d, then 200 mg/m^2 12-hrly (under investigation in PACTG protocol 356) **> 2 mo.:** 120 mg/m^2 qd x 14 d, then 120 - 200 mg/m^2 (maximum 200 mg) 12-hrly OR 7 mg/kg 12-hrly if < 8 yrs and 4 mg/kg 12-hrly if > 8 yrs **Adolescents:** 200 mg qd x 14 d, then 200 mg 12-hrly	Skin rash (including Stevens-Johnson), fever, nausea, headache, elevated hepatic transaminases, hepatitis (can be severe or fatal), hypersensitivity reactions	Can be given with food Store suspension at room temp. and shake well before use WARN PARENTS ABOUT RASH Do not escalate dose if rash occurs (for mild-moderate rash, hold drug until rash clears, then restart dosing from beginning of escalation); if severe rash, discontinue drug Increase NVP dose by about 30% if coadministered with rifampicin Drug interactions
Protease inhibitors			
Lopinavir/ritonavir (LPV/RTV, LPV/r, Kaletra) 80 mg LPV/20 mg RTV per ml sol 133.3 mg LPV/33.3 mg RTV per cap	**< 6 mo.:** 300 mg/m^2 LPV/75 mg/m^2 RTV is under investigation (PACTG protocol 1030) but dose escalation may be necessary **≥ 6 mo. and 7 - < 15 kg:** 12/3 mg/kg bid **15 - 40 kg:** 10/2.5 mg/kg bid **> 40 kg:** 400/100 bid OR (for all weights ≥ 7 kg and age ≥ 6 mo.) 230/57.5 mg/m^2 bid (max. 400/100 mg) With efavirenz or nevirapine: **< 6 mo.:** No data **≥ 6 mo. and 7 - < 15 kg:** 13/3.25 mg/kg bid **15 - 50 kg:** 11/2.75 mg/kg bid **≥ 50 kg:** 533/133 mg bid OR (for all weights ≥ 7 kg and age ≥ 6 mo.) 300/75 mg/m^2 bid (max. 533/133 mg)	Diarrhoea, headache, asthenia, and nausea and vomiting, hyperlipidaemia, hypercholesterolaemia, rash in patients receiving LPV/r with other ARV drugs, spontaneous bleeding episodes in haemophiliacs, pancreatitis, hyperglycaemia, ketoacidosis, diabetes, and hepatitis	Oral solution and capsules should be preferably refrigerated; however can store at room temperature (up to 25°C) for 2 months Liquid formulation has alcohol, low volume, but bitter taste Capsules are large, tablet form under investigation Take with food Numerous drug interactions
Nelfinavir (NFV, Viracept) 200 mg/tsp pwdr 50 mg per one level gram scoop 250, 625 mg tabs	**Newborn:** 40 mg/kg bid is under investigation (PACTG protocol 353)† **2 - 6 yrs:** 20 - 30 mg/kg tid is the FDA-approved dose, but doses up to 45 mg/kg tid are routinely used **> 6 yrs:** 55 mg/kg bid **Adolescents:** 750 mg tid OR 1 250 mg bid OR 1 500 mg bid under study †not FDA approved under 2 yrs	Diarrhoea, asthenia, abdominal pain, rash, and exacerbation of chronic liver disease, spontaneous bleeding episodes in haemophiliacs, hyperglycaemia, ketoacidosis, and diabetes	Powder is sweet, faintly bitter, but gritty and hard to dissolve; reconstitute immediately before administration in water, milk, formula, pudding, etc.; avoid mixing with acidic food or juice (increases bitter taste) Crushed tablets may be preferred (even for infants) given difficulties with powder formulation if appropriate dose can be given Store powder and tablets at room temperature Take with food. Drug interactions

*All doses are oral unless otherwise noted. Adapted from NIH Guidelines (**http://www.aidsinfo.nih.gov**), manufacturer prescribing information, and WHO Guidelines for Scaling Up Antiretroviral Therapy.

glucuronidation to zidovudine-glucuronide, which is then excreted renally. Zidovudine pharmacokinetics have been studied in a wide range of paediatric populations from preterm infants to adolescents, demonstrating rapid increases in clearance during the first few weeks of life with smaller increases throughout the first 2 years of life. Zidovudine has the shortest half-life of the NRTIs and requires at least twice-daily administration. The initial dose of 8 mg/kg/d in divided doses is increased to 160 mg/m^2 8-hourly at 6 - 12 weeks of age. Bone marrow suppression, presenting as anaemia and neutropenia, are the most prominent adverse effects and are more frequently seen with higher zidovudine concentrations.

LAMIVUDINE

Lamivudine is a cytidine analogue that is widely used in children and adults. In general it is one of the most well-tolerated agents in this class. Lamivudine undergoes minor liver metabolism to the inactive trans-sulphoxide metabolite. The primary route of elimination is renal, which is initially immature in the neonate and requires reduced dosing in this population. The primary route of elimination is renal, which is initially immature in the neonate, and lamivudine requires reduced dosing in this population.[1,2]

STAVUDINE

Stavudine is a widely available thymidine analogue, but its pharmacokinetic fate has not been fully elucidated. About 60% of the drug is eliminated via endogenous pathways while 40% is renally eliminated via filtration and active tubular secretion.[3] Decreased renal function in the neonate suggests that a reduced dosage may be needed initially. The dosage of stavudine is based on whether the child weighs less than or more than 30 kg. Dosages of 0.5 - 1 mg/kg/d across a wide age range in children produced equivalent exposure to that achieved in adults.[4] Coadministration of stavudine with zidovudine is not recommended owing to competitive intracellular phosphorylation and thus potential loss of activity. Its combination with didanosine is also to be avoided owing to increased toxicities. The paediatric oral solution requires refrigeration, given that in one study significant loss

TABLE II. PAEDIATRIC PHARMACOKINETIC PROPERTIES OF COMMONLY AVAILABLE ANTIRETROVIRAL AGENTS*

Drug	Age group	Primary elimination route	CL/F (l/h/kg)	$T_{\frac{1}{2}}$ (h)	Food effect on absorption	Protein binding	Reference
Zidovudine	Premature neonates 4 - 7 d < 30 wks GA: > 30 wks GA: Premature neonates 4 - 8 d Premature neonates 10 - 25 d Term neonates 1 - 13 d Infants & children 6 mo. - 12 yrs	Hepatic: UGT > Renal	 0.09 0.13 0.14 ± 0.35 0.26 ± 0.35 0.65 ± 0.29 1.8	 7.3 ± 1.9 4.4 ± 1.5 3.1 1.5	Minimal	Low	Capparelli[21] Hoody[20]
Lamivudine	Neonates 7 d Children 5 mo. - 17 yrs	Renal	0.40 0.77	6 2.1	None	Low	Hoody[20]
Stavudine	Children 5 wks - 15 yrs	Renal	0.83 ± 0.26	0.96	None	Low	Package insert[3]
Didanosine	Infants ≤ 120 d Children 3 mo. - 18 yrs	Renal & Hepatic: PNP	57 ± 30 (l/h/m^2) 152.5 ± 81.7 (l/h/m^2)	 0.93 ± 0.43	Food ↓	Low	Kovacs[7] Stevens[6]
Abacavir	Children 3 mo. - 13 yrs	Hepatic: ADH & UGT	0.95	1.28	None	Moderate	Hoody[20]
Nevirapine	Neonates (single dose) Infants & children 1 mo. - 16 yrs	Hepatic: CYP3A, CYP2B6	0.033 0.10 + 0.06	37	None	Moderate	Mirochnick[22] Capparelli[23]
Efavirenz	Children 4 - 16 yrs	Hepatic: CYP3A, CYP2B6	0.19		Avoid high-fat meals	High	Hoody[20]
Nelfinavir	Infants 2 - 8.5 mo. Children 2 - 14 yrs	Hepatic: CYP3A, CYP2C19	4.2 1.5	2.6	Food (high fat) ↑	High	Litalien[24] Hoody[20]
Lopinavir/ ritonavir	Children 6 mo. - 12 yrs	Hepatic: CYP3A	2.57 ± 5.25 (l/h/m^2)	7.6 ± 5.1	Food ↑	High	Saez-Llorens[15]
Tenofovir	Children 6 - 16 yrs	Renal	32 ± 16.3 (l/h/m^2)	12.5	Food ↑	Low	Hazra[25]

* All values are means ± standard deviation.

CYP = cytochrome; UGT = uridine glucuronyl transferase; ADH = alcohol dehydrogenase; PNP = purine nucleoside phosphorylase.

of stability was observed after 4 weeks at 25°C.[5] Instead, capsules may be opened and mixed with a small amount of food or liquid before administration.

DIDANOSINE

Didanosine is an inosine analogue that requires intracellular phosphorylation for activity in resting cells. It has a long intracellular half-life of 25 - 40 hours, which allows for once-daily dosing. Didanosine is rapidly degraded in acidic media necessitating coadministration with buffering agents or antacids for optimal absorption. Didanosine should therefore ideally be given without food or 2 hours after a meal for optimal absorption. However, this may be impractical for young children who feed frequently. A study of didanosine with and without food in children showed modest reductions in peak concentrations.[6] It is eliminated through metabolism similar to that of endogenous purines as well as renal pathways.

Infants younger than 7 months of age have lower didanosine clearance than older children. As a result of reduced clearance, infants 2 weeks - 4 months of age may benefit from a smaller dosage initially to avoid risk of didanosine toxicity.[7,8]

Didanosine should not be given with stavudine or zalcitabine to avoid overlapping toxicities of peripheral neuropathy and pancreatitis. The liquid formulation needs to be prepared with antacid. After reconstitution, the oral solution is stable at temperatures up to 35°C for 8 weeks.[5]

OTHER NUCLEOSIDES

Other NRTI members that are not generally available in Africa include abacavir, emtricitabine, and the nucleotide analogue, tenofovir. Briefly, emtricitabine is a cytidine nucleoside analogous to lamivudine with a longer plasma half-life. Abacavir is a guanosine analogue with synergy to zidovudine and lamivudine but clinically low activity in highly treatment-experienced patients. While generally well tolerated, a potentially fatal hypersensitivity reaction can occur in up to 5% of children.[9] Tenofovir is an acyclic nucleotide prodrug that is converted into the active triphosphate intracellularly. Its ability to produce rapid reduction in viral replication has generated interest in it as a potential therapy to prevent MTCT. It can cause nephrotoxicity and it also has drug interactions with didanosine, lopinavir and atazanavir.[10]

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

NNRTIs inhibit the HIV-1 reverse transcriptase at a non-competitive site on the enzyme and, unlike the NRTIs, do not require intracellular activation. NNRTIs are potent agents, but the entire class can be rendered inactive by a single resistance mutation in the RT gene. NNRTIs are lipophilic, moderately to highly protein bound, and widely distributed. They undergo hepatic metabolism via CYP2B6 and CYP3A4 inducing their own metabolism. Hepatotoxicity is a class adverse effect that requires routine liver function monitoring.

NEVIRAPINE

Nevirapine has been used extensively in neonates and children. It is well absorbed and does not require food for optimal absorption. Nevirapine is highly lipophilic and widely distributed including crossing the placenta. It is also a CYP3A4 inducer that can increase the clearance of other coadministered CYP3A4 substrates, including protease inhibitors. Nevirapine oral clearance is age-dependent. In neonates the half-life of nevirapine is prolonged with clearance doubling over the first month of life.[11] This long half-life allows HIV-suppressive concentrations to be maintained for 2 weeks with a single dose to the mother followed by a single dose to infants at 4 - 5 days of life. Older infants and children appear to have greater nevirapine clearance than adults.[12] The nevirapine dose is given twice as frequently after the first 2 weeks of therapy to account for the autoinduction of its metabolism.

Nevirapine therapy can cause hepatotoxicity and severe hypersensitivity reactions. Hepatic dysfunction usually occurs within the first few months of therapy, can be fatal and occurs more frequently in adults with elevated baseline liver transaminases, hepatitis B or C coinfection, and higher CD4 counts. Women are also at a higher risk for nevirapine-induced hepatotoxicity; pregnant women with CD4 counts > 250 cells/µl have a 12-fold greater risk for hepatotoxicity.[13] Nevirapine can also cause severe, life-threatening skin reactions, some resulting in death, including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis.

Paediatric dosing for nevirapine has been based on both body surface area (BSA) and milligram per kilogram methods. The weight-based dosing results in wider variability in exposure than the BSA dosing. Weight-band dosing, linked to available formulation sizes, has been developed to match the BSA dosing and improve exposure without calculating BSA.

EFAVIRENZ

Efavirenz has been used extensively in children over 3 years of age with excellent success. In older children it is well absorbed and can be given once daily owing to its long half-life. Pharmacokinetic data are sparse in children under 3 years of age, but initial studies suggest that larger doses of the suspension may be needed. If given with rifampicin, a modest increase in the dose of efavirenz is suggested. Frequently in adults, and in up to 14% of children, efavirenz causes central nervous system side-effects. Bedtime administration of efavirenz is advocated to possibly decrease the impact of side-effects.[14] It can be given without regard to food, although high-fat meals are discouraged in adults to avoid an increase in adverse effects from increased absorption.

PROTEASE INHIBITORS (PIs)

PIs block the HIV-1 protease enzyme, which results in the formation of immature viral proteins incapable of

transmission to non-infected host cells. Unlike the NNRTIs, resistance to PIs requires multiple mutations to render this class useless.

Only two PIs are likely to be encountered in resource-limited environments. Most PIs do not have adequate paediatric formulations or have a high pill burden, and need at least twice-daily dosing. All members of this class have variable oral absorption which is dependent on dosing in the presence or absence of food, and even on the composition of food intake. They exhibit incomplete and variable absorption, are highly protein bound and achieve only limited penetration into the CSF and across the placenta. They undergo extensive phase I oxidative metabolism primarily via CYP3A4. PIs are well-known substrates of CYP3A4 and some are also potent inhibitors of this system. This results in a large number of drug interactions with other ARVs and antituberculosis agents.

Drug-drug interactions with PIs are well recognised in adults and probably occur in children as well. Fortunately PIs can be combined to produce greater potency and durability, often taking advantage of positive pharmacokinetic drug interactions, without concern for the antagonist drug activity that plagues members of the NRTI class. A disadvantage of PIs is a higher incidence of gastrointestinal adverse effects that can negatively affect drug tolerability, adherence and absorption. Increasingly, PIs have also been linked to metabolic complications such as glucose intolerance, insulin resistance, hyperlipidaemia and lipodystrophy. The impact of these effects on paediatric growth and development is unknown.

LOPINAVIR/RITONAVIR

Lopinavir/ritonavir is a PI co-formulated with a small dose of a pharmacokinetic enhancing agent, ritonavir. Ritonavir is a potent inhibitor of CYP3A4, which increases the lopinavir plasma exposure and half-life of lopinavir allowing for twice-daily administration. Food enhances lopinavir absorption. Lopinavir is highly protein bound and is hepatically metabolised with very little renal elimination. In a study of children between 6 months and 12 years of age, a dose of 230/57.5 mg/m^2 or 300/75 mg/m^2 twice daily with nevirapine achieved similar lopinavir exposure to adults.[15] Limited data in younger infants suggest high variability in absorption and elimination. This variability may make this agent difficult to use in young infants.[16]

Lopinavir is available in a bitter paediatric oral solution that is taken with food for optimal absorption. The oral solution also contains 42% alcohol and requires refrigeration. Exposure to excessive heat is discouraged, and if left at room temperature (25°C) the solution or capsules must be used within 2 months. While both formulations appear to retain potency for brief periods of time at temperatures up to 45°C, the current gelcap formulation fuses together making them unusable.[17]

NELFINAVIR

Nelfinavir was the first PI well studied in paediatric patients. High-fat meals enhance absorption and large doses are needed in infants to achieve adequate exposure. Most practitioners crush tablets for young children rather than administer the powder formulation, owing to inconsistent absorption of the powder. Neither formulation requires refrigeration. Nelfinavir, however, is poorly absorbed in the absence of food and erratic feeding patterns and changes in gastrointestinal motility can also dramatically decrease oral bioavailability. It is metabolised to an M8 active metabolite via CYP2C19 and is also metabolised by CYP3A. Pharmacokinetic studies of nelfinavir have demonstrated a rapid oral clearance in very young children, requiring larger mg/kg daily doses than adults to attain similar exposure to that in adults.[18-20]

SUMMARY

Half of the ARV agents available worldwide have paediatric approval, but many are without ideal paediatric formulations. Pharmacokinetic differences in paediatric populations require careful attention to dosing and concomitant therapies. Importantly, ARV therapy can be limited by short-term and long-term toxicity and drug interactions.

Low-cost, sustained and consistent access to ARV therapy is necessary to combat the HIV epidemic. For optimal response > 90 - 95% adherence to ARVs is required. This requires that extensive education and support resources be provided in addition to the ARV medications themselves. Paediatric patients receiving ARV therapy require ongoing monitoring to ensure tolerability, dose adjustments with advancing age, acceptability and therapeutic success.

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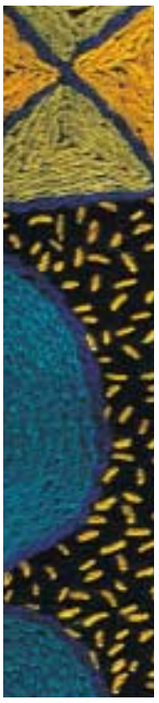

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