REVIEW ARTICLE

Drug Safety 2002; 25 (14): 973-991
0114-5916/02/0014-0973/$25.00/0

Tolerabilities of Antiretrovirals in Paediatric HIV Infection

Daniel Avi Lemberg, Pamela Palasanthiran, Michele Goode and *John B. Ziegler*

Department of Immunology and Infectious Diseases, Sydney Children's Hospital, Randwick, New South Wales, Australia

Contents

Abstract

Data on the efficacy and tolerability of antiretrovirals in children are limited as, in contrast to adult studies, large paediatric cohort studies are lacking. Thus, data pertaining to adults are often extrapolated to children despite the acknowledgement that children are not little adults. This review summarises information gathered from existing reports and focuses on the tolerabilities of antiretrovirals in children infected with HIV-1. The efficacy of antiretrovirals is not included in the scope of the discussion.

Taste of antiretrovirals should be an important factor when considering the tolerability of antiretrovirals in children. However, antiretroviral options are often limited in young children as only some of the antiretrovirals are available as paediatric formulations. All antiretrovirals have been associated with toxicities in children, but in general, they are relatively well tolerated. The gastrointestinal system including hepatic system is most prone to being affected by these drugs.

Skin rashes and hypersensitivity reactions are also associated with antiretroviral use, particularly with the non-nucleoside reverse transcriptase inhibitors. Mitochondrial toxicities that lead to impairment of liver function, pancreatic function and lactic acidosis are associated with most of the nucleoside analogues. Haematological toxicity is often a dose limiting adverse effect especially of the nucleoside analogues, in particular zidovudine. The protease inhibitors are associated with gastrointestinal intolerance (diarrhoea) and metabolic derangements that can lead to hypercholesterolaemia and hypertriglyceridaemia, which in turn and can lead to changes in body habitus. The renal system is also affected by several drugs, the most important of which is indinavir, which has been associated with renal stones and damage to the renal tubules.

Fortunately, with lower incidence of major toxicity and with the range of drugs now available for paediatric use, toxicities are usually not a barrier to effect antiretroviral therapy in children.

Internationally, the occurrence of HIV infection is continuing to increase at a great rate. In 2001 it was estimated that there were 5 million new HIV infections throughout the world, i.e. 14 000 new HIV infections a day. This 5 million includes 1.8 million women and 800 000 children. Resource-poor countries, particularly those in sub-Saharan Africa remain the main contributor to the numbers of new HIV infections both in children and adults.[1]

In developed countries perinatal transmission of HIV is becoming rare. In some circumstances with maximal therapy, perinatal transmission rates have been reduced to <1%. Nevertheless, with the increasing abilities and necessities of populations to travel across continents and countries, most paediatricians will at some stage during their career be required to manage children with HIV infection. They will need to be familiar with the principles of management and the tolerabilities of the drugs used in the treatment of HIV infection.

When available, highly active antiretroviral therapies (HAART) have had a dramatic impact on the natural history of paediatric HIV infection. Martino et al.[2] presents data that show a dramatic increase in the cumulative survival probability of children treated with HAART. These therapies involve multiple drugs and have increased the complexities of managing children with HIV infection. This paper presents information on a range of different drugs and their toxicities used in the treatment of children and/or adults with HIV infection.

1. Nucleoside Reverse Transcriptase Inhibitors

1.1 Thymidine Analogues

1.1.1 Zidovudine

Zidovudine (2′,3′-azido-3′-deoxythymidine), the oldest and most widely prescribed of the reverse transcriptase inhibitors in paediatric HIV infection, is one of the more palatable antiretroviral agents. It is available as a strawberry flavoured suspension at a concentration of 10 mg/ml or in capsules of 100 and 250mg, or packaged as a combination tablet of zidovudine 300mg and lamivudine 150mg. Its high oral bioavailability (70%) means oral doses are only 50% higher than intravenous doses. Its cerebrospinal fluid (CSF) **:** serum ratio of 0.25 is the highest of the nucleoside analogues.[3] In early studies, oral zidovudine was given in three or four divided daily doses due to the short plasma half-life (1.5 hours). However, as the half life of the active intracellular zidovudine triphosphate is longer, the drug is given 12-hourly in combination therapies in both adults and children.[4-6]

In animal studies, zidovudine was associated with an increased risk of both liver and lung tumours.[7,8] Zidovudine has been listed as a US Food and Drug Administration (FDA) pregnancy category C drug and a category B3 drug in Australia (tables I and II). However, when given to mothers

Table I. US Food and Drug Administration categorisation of HIV antiretrovirals relating to use in pregnancy

Drug	Pregnancy category
Nucleoside/nucleotide analogue reverse transcriptase inhibitors	
Thymidine analogues	
Zidovudine	C
Stavudine	C
Non-thymidine analogues	
Lamivudine	C
Didanosine	B
Zalcitabine	C
Abacavir	C
Non-nucleoside reverse transcriptase inhibitors	
Nevirapine	C
Delavirdine	C
Efavirenz	C
Protease inhibitors	
Ritonavir	B
Saquinavir	B
Indinavir	C
Nelfinavir	B
Lopinavir	C

B = no effect in humans with adverse effects in animals OR no effects in animals without human data; **C** = adverse effects in animals without human data OR no data available for animals or humans.

infected with HIV, zidovudine has not resulted in any teratogenic effects.[9]

The early clinical paediatric trials of zidovudine (AIDS Clinical Trials Group [ACTG] 043) were performed without a placebo control group as efficacy had been established in adults.[10] Zidovudine given via continuous intravenous infusion was relatively well tolerated in children. Nausea, vomiting, and headache in the first weeks after initiating zidovudine resolved with time and without withdrawal of treatment or reduction in dosage.[8,11] Subjective and self limiting symptoms of gastrointestinal intolerance, headache, insomnia and asthenia were seen mainly in adults and adolescents.[11]

Comparable with adults, the most significant adverse effects of zidovudine in children were the haematological toxicities, with anaemia and neutropenia being the most significant. These toxicities have been reduced with twice daily administration. The anaemia secondary to zidovudine therapy is macrocytic; in some studies, measurement of mean corpuscular volume (MCV) has been used to follow compliance with zidovudine therapy.[12,13]

Initial studies of zidovudine were performed with a dosage of 180 mg/m^2 per dose as four doses per day. However, further studies show that a similar efficacy can be achieved with doses of 90 mg/m^2 per dose. This smaller dose has resulted in a smaller proportion of patients with significant neutropenia (i.e. grade 3 toxicity, table III) with 9.5% experiencing anaemia of grade 3 toxicity or more, while 28.8% had absolute neutrophil counts of less than 650/m^3.[14] In another phase II study, of the 88 children studied, 26% had downward adjustments or interruptions in their dose of zidovudine secondary to anaemia or neutropenia.[10] A review by Palasanthiran et al.[15] of 113 patients in five studies revealed that 23% required packed cell transfusions for anaemia which was the main reason for dosage adjustment or cessation.

In the neonate there is concern that coadministration of zidovudine with cotrimoxazole (trimethoprim-sulfamethoxazole) will increase the likelihood of haematological toxicity via an additive marrow suppressive effect.[9] This effect can be minimised by giving cotrimoxazole every second day instead of daily, reducing the grade 3 haematological toxicities from 42–24%.[16]

Zidovudine crosses the placenta efficiently, impacting on the transmission of HIV virus from mother to fetus. In the ACTG 076 trial there were no congenital malformations associated with zidovudine therapy. The haemoglobin levels at birth in infants of mothers treated with zidovudine were significantly decreased compared with those not treated. The effect was not prolonged and there was no statistically significant difference in haemoglobin levels between the two groups at 12 weeks of age.[17]

Zidovudine inhibits DNA polymerase-γ, an enzyme required for mitochondrial replication. This pathway is the mechanism by which tissues with

Table II. Australian categorisation of HIV antiretrovirals relating to use in pregnancy

Drug	Pregnancy category
Nucleoside/nucleotide analogue reverse transcriptase inhibitors	
Thymidine analogues	
Zidovudine	B3
Stavudine	B3
Non-thymidine analogues	
Lamivudine	B3
Didanosine	B2
Zalcitabine	D
Abacavir	B3
Non-nucleoside reverse transcriptase inhibitors	
Nevirapine	B3
Delavirdine	B3
Efavirenz	D
Protease inhibitors	
Ritonavir	B3
Saquinavir	B1
Indinavir	B3

B1 = drugs that have been taken by only a limited number of pregnant women and women of childbearing age without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage; **B2** = drugs that have been taken by only a limited number of pregnant women and women of childbearing age without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking but available data show no evidence of an increased occurrence of fetal damage; **B3** = drugs that have been taken by only a limited number of pregnant women and women of childbearing age without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage the significance of which is considered uncertain in humans; **D** = drugs that have caused, are suspected to have caused or may be expected to cause an increased incidence of fetal malformation or irreversible damage. These drugs may also have adverse pharmacological effects.

high mitochondrial content are damaged secondary to zidovudine therapy. Mitochondrial toxicity has been noted in the liver, heart and muscle in adults.[9] Walter et al.[18] studied 87 children with HIV infection taking zidovudine and showed that 83% had at least a minor elevation in creatinine kinase (CK) level (>65 IU/L) whereas 21% had a CK level of >260 IU/L. There was no clinical evidence of myopathy in these children and no dosage adjustment or modifications were made on the basis of elevated CK levels.[18]

Cardiomyopathy has been reported to be associated with zidovudine therapy in adults. An early study in HIV-infected children treated with zidovudine did not demonstrate any change in cardiac function.[19] Subsequently a study by Domanski et al.[20] found that the odds ratio for cardiomyopathy developing was 8.5 times greater in children exposed to zidovudine therapy compared with children not exposed to the drug. Zidovudine-treated children had a lower average fractional shortening when adjusted for period of HIV infection, age and CD4+ count.[20] Further studies of zidovudine suggest a high incidence of cardiac problems including congestive cardiac failure, hypotension, hypertension, dysrhythmias, progressive cardiac dilatation and hypertrophy as well as changes in cardiac structure and wall stress.[19,21] Withdrawal of zidovudine is advised in the event of symptomatic cardiac dysfunction. Cardiomyopathy is an indication to change treatment regimen, as this development may be secondary to zidovudine therapy or due to uncontrolled HIV-1 infection, suggesting HIV-1 resistance to zidovudine.[19,21,22]

In a study of (uninfected) infants exposed to zidovudine *in utero* by Blanche et al.,[23] eight patients out of 1754 from the French National Epidemiological Network for Studying Mother to Child transmission of HIV-1 had mitochondrial dysfunction. Six of the eight patients had neurological symptoms that included seizures, quadripareses, cognitive impairment, brain stem symptoms and myopathy. Five of the patients had persistently increased blood lactate concentrations, consistent with mitochondrial respiratory chain dysfunction. There has also been a report of severe transient lactic acidosis in a neonate treated with zidovudine suggesting mitochondrial dysfunction.[24] Longer term studies have shown abnormalities of myelinisation, persistent lactic acidosis and electroretinographic findings, all thought to be secondary to mitochondrial abnormalities.[25] Abnormal liver transaminase levels and severe hepatotoxicity have

Table III. Grading the severity of paediatric (>3 months of age) adverse events: modified from the paediatric AIDS clinical trial group (PACTG) recommendations

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Haematology				
Haemoglobin (g/dl) [>3 months to >2 years]	9.0–9.9	7.0–8.9	<7.0	Cardiac failure secondary to anaemia
Haemoglobin (g/dl) [≥2 years]	10–10.9	7.0–9.9	<7.0	Cardiac failure secondary to anaemia
Absolute neutrophil count	750–1 200	400–749	250–399	<250
Platelet count		50 000–75 000	25 000–49 000	<25 000 or bleeding
Prothrombin time	1.1–1.25 × N	1.26–1.5 × N	1.51–3.0 × N	>3 × N
Partial thromboplastin time	1.1–1.66 × N	1.67–2.33 × N	2.34–3.0 × N	>3 × N
Gastrointestinal				
Bilirubin	1.1–1.9 × N	2.0–2.9 × N	3.0–7.5 × N	>7.5 × N
AST	1.1–4.9 × N	5.0–9.9 × N	10.0–15.0 × N	>15.0 × N
ALT	1.1–4.9 × N	5.0–9.9 × N	10.0–15.0 × N	>15.0 × N
γ-Glutamyl transferase	1.1–4.9 × N	5.0–9.9 × N	10.0–15.0 × N	>15.0 × N
Pancreatic amylase	1.1–1.4 × N	1.5–1.9 × N	2.0–3.0 × N	>3.0 × N
Total amylase + lipase	1.1–1.4 × N	1.5–2.4 × N	2.5–5.0 × N	>5.0 × N
Uric acid	7.5–9.9	10–12.4	12.5–15.0	>15.0 or gout
CPK	See Neuromuscular			
Abdominal pain	Mild	Moderate – no treatment needed	Moderate – treatment needed	Severe – hospitalisation and treatment
Diarrhoea	Soft stools	Liquid stools	Liquid stools and mild dehydration – bloody stools	Dehydration requiring intravenous therapy or hypotensive shock
Constipation	Mild	Moderate	Severe	Distension and vomiting
Nausea	Mild	Moderate – decreased oral intake	Severe – little oral intake	Unable to ingest food or fluid for >24 hours
Vomiting	<1 episode/day	1–3 episodes/day or duration >3 days	>3 episodes/day or duration >7 days	Intractable vomiting
Neuromuscular				
Myopathy or neuromuscular junction impairment	Normal or mild (<2 × N) CPK elevation	Mild proximal weakness and/or atrophy not affecting gross motor function. Mild myalgias, ± mild CPK elevation (<2 × N)	Proximal muscle weakness and/or atrophy affecting motor function ± CPK elevation; or severe myalgias with CPK >2 × N; consider confirmatory EMG and/or muscle biopsy	Onset of myasthenia-like symptoms (fatigable weakness with external, variable ophthalmoplegia and/or ptosis), or neuromuscular junction blockade (acute paralysis) symptoms (confirm with EMG) or grade 3 symptoms which do not resolve on dose adjustment; confirm with muscle biopsy
Cutaneous				
Rash		Diffuse maculo-papular rash, dry desquamation	Vesiculation, ulcers	Exfoliative dermatitis, Stevens-Johnson or erythema multiforme, moist desquamation

CPK = creatine phosphokinase; **EMG** = electromyogram; **N** = normal value.

been reported as a secondary effect of zidovudine in paediatric patients. Brady et al.[14] noted that 17% of children in their study had either one or both of the liver transaminase levels elevated after treatment.

Zidovudine is metabolised to glucuronide azidothymidine by the liver cytochrome P450 (CYP) system. Glucuronide azidothymidine is almost completely excreted by the kidneys. Kidney dysfunction or drugs (such as indinavir) that interfere with renal excretion can alter the half-life of the active metabolite. The half life of zidovudine in neonates under 2 weeks of age is prolonged due to the immature glucuronide function of the neonatal liver.[4,26-28]

Zidovudine can cause nail dyschromia. In one retrospective study of adults, 16 of 38 patients receiving zidovudine therapy had nail discolouration.[29] Although not reported in children there is a case report of severe paronychia secondary to neutropenia in a neonate.[30]

1.1.2 Stavudine

Stavudine, a pyrimidine nucleoside analogue with potent anti-HIV activity, is available as a paediatric powder and can be reconstituted to a concentration of 1 mg/ml, or can be sprinkled onto soft food.[31] It also comes in capsule sizes of 15, 20, 30 and 40mg. Stavudine undergoes intracellular triphosphorylation by human cellular kinases to its active form stavudine triphosphate which is a competitive inhibitor of HIV reverse transcriptase and a DNA chain terminator.[8] Zidovudine and stavudine are reported to be antagonistic, due to the inhibition of intracellular phosphorylation of stavudine by zidovudine[13] and are therefore not recommended for use together in combination therapies.[32]

A phase I/II trial of oral stavudine documented oral bioavailability of 61–78%.[33] Stavudine is renally excreted and has a serum half-life of 1 hour and an intracellular half-life of 3.5 hours. Of an administered dose of stavudine, 24–50% is recovered unchanged in the urine, with the remainder changed in the liver.[11] CSF concentrations range from 16–97% of plasma concentrations. This is not as consistent as CSF concentrations obtained with zidovudine.[33] In animal models, stavudine is well transported across the placenta. Stavudine is a US FDA pregnancy category C drug (table I), and is an Australian pregnancy category B3 drug (table II).

The relative risk of incurring haematological toxic events was 2.2 for zidovudine recipients compared with those receiving stavudine. The annual rate of any haematological abnormality was 12% in the stavudine group and 22% in the zidovudine group.[31] Anaemia requiring dose interruption occurred at much lower levels than that seen in previous studies with zidovudine. The anaemia is similarly macrocytic with a rise in MCV.[33]

Stavudine causes biochemical abnormalities including elevation of liver transaminase levels as well as gastrointestinal symptoms such as nausea and abdominal pains. These toxicities occur at similar rates to those seen with zidovudine therapy.[31]

Peripheral neuropathy, one of the dose limiting toxicities observed in HIV-infected adults, has not yet been observed in young children.[31,33] This toxicity is more likely to occur with longer duration of therapy. The majority of adults with peripheral neuropathy had a predisposing condition.[34] Adolescents are considered at relatively higher risk of peripheral neuropathy than younger children.[11]

Hepatic steatosis and lactic acidosis is a rare adverse effect of stavudine use described in adolescents, and less commonly in younger children. This syndrome is hypothesised to be caused by mitochondrial injury. Stavudine as with other nucleoside analogues leads to depletion of mitochondrial DNA plus selective inhibition of DNA polymerase-γ (responsible for replication of mitochondrial DNA). Depletion of this DNA leads to depletion of the oxidative phosphorylation system, causing a defect in pyruvate metabolism leading to production and accumulation of lactate. This syndrome is associated with an elevated serum lactate level, hepatic steatosis, occasionally pancreatitis and more commonly myopathy.[35] Although a relatively rare toxicity it is important to monitor hepatic transam-

inase levels 3–4 monthly while patients are receiving stavudine therapy. If there is significant elevation in these levels, then levels of serum lactate, pancreatic and muscle enzymes should be measured.

1.2 Non-Thymidine Analogues

1.2.1 Lamivudine

Lamivudine is a reverse transcriptase inhibitor and has the advantage of less pronounced inhibition of mammalian DNA polymerase. Lamivudine can be given orally in a suspension of 10 mg/ml or administered in tablets of 150mg. The pharmacokinetics of both the combination zidovudine plus lamivudine tablets and lamivudine alone were not altered by administration with meals and the lamivudine can be administered with or without food.[36] Lamivudine is also available as part of a recently licensed combination tablet with a fixed composition of zidovudine 300mg, lamivudine 150mg and abacavir 300mg.

Lamivudine undergoes anabolic phosphorylation by intracellular kinase to form lamivudine 5-triphosphate, the active anabolite which prevents HIV-1 replication by competitively inhibiting viral reverse transcriptase and terminating proviral DNA chain extension.[37] The plasma half life of lamivudine is approximately 1.7 hours.[38] The serum half life and oral bioavailability are decreased in children (by 68%) when compared with adults.[37,38] The intracellular half life of the active 5′- triphosphate anabolite is 10.5–15.5 hours in children. CSF concentration ratio is 0.11 that of the serum concentration. CSF penetration is less than that seen with zidovudine but greater than that with didanosine.[3]

Lamivudine is well tolerated and has a palatable taste. Adverse effects are not dose related. Lamivudine crosses the placenta and significant concentrations are found in amniotic fluid, umbilical cord and neonatal serum and it is also secreted into breast milk. Lamivudine is primarily renally excreted and renal impairment requires dose modification when creatinine clearance falls below 50 ml/min.[39] Hepatic impairment does not affect the pharmacokinetics of lamivudine. Trimethoprim decreases the renal clearance of lamivudine prolonging its half life.[37]

As with other non-thymidine nucleoside reverse transcriptase inhibitors, hepatic toxicity is a major adverse effect associated with lamivudine. In a study by Lewis et al.,[38] three of 89 patients had lamivudine therapy withdrawn due to grade 4 toxicity, i.e. a greater than ten times increase in serum transaminase levels. One of these children continued to have hepatic dysfunction 10 months after stopping the drug. One child became ataxic and one experienced mild peripheral neuropathy. Almost all these events resolved with discontinuation of treatment. Seven of 89 children developed chemically apparent pancreatitis, while another two developed asymptomatic elevations of amylase and lipase. None of these events of pancreatitis resulted in death of the child.[38] Pancreatitis occurred in patients with advanced symptomatic HIV disease. Parents noted an increase in energy and activity of children participating in the study. Two of these had behaviour changes that interfered with normal school and home functions. The associated increase in appetite and energy together with a low rate of toxicity make lamivudine a valuable antiretroviral in children with HIV infection.

Lamivudine has been used in the treatment of hepatitis B infections and in a study by Sokal et al.[39] the most common adverse events were minor. In this study of 53 patients there were no adverse liver, pancreatic or haematological toxicities. This suggests that the toxicities seen in the previous study of lamivudine in children with HIV infection are contributed to by previous antiretroviral treatments and/or advanced HIV infection.

There does not seem to be any pharmacokinetic interaction between zidovudine and lamivudine. In a small study by Horneff et al.,[40] combination therapy with zidovudine and lamivudine was well tolerated by children. Compliance was excellent as evidenced by increases in MCV. There were no adverse effects that required discontinuation of drugs. Almost 40% of the patients had an increase

in amylase activity. As there were no clinical signs of pancreatitis and dosage adjustment was not required.

1.2.2 Didanosine

Didanosine (2′3′-dideoxyinosine) for children is supplied as a sterile freeze-dried powder and can be reconstituted to solutions of 10 mg/ml or 5 mg/ml. Since didanosine is acid labile, oral doses must include an antacid and should be given at least 30 minutes before a meal.[8,41] A delayed-release formulation in the form of enteric-coated beadlets has recently become available. Didanosine has a short plasma elimination half life, ranging from 0.5–2.74 hours in adults and symptomatic children and the intracellular half-life of the active moiety dideoxy adenosine triphosphate (ddATP) is longer (>25 hours). It has poor oral bioavailability (20%).[4,42] There is significant variability in absorption and poor penetration into the CNS (CSF : serum ratio of 0.05) limiting its use in children with HIV encephalopathy.[4,43,44] Total body clearance of didanosine is significantly reduced in HIV-infected patients with impaired renal function necessitating a change in dosage.[42,45] Inter-patient variability in drug levels post-didanosine administration is related to the amount of antacid that each patient requires for optimal absorption of didanosine. The use of the enteric coated formulation of didanosine is anticipated to minimise this problem in future. The alkaline environment affects the absorption of other therapies used in children with HIV, such as ketoconazole, isoniazid and dapsone. These interactions can be avoided by administering the buffered didanosine 1–2 hours after the other drugs.[8]

The major toxicity of didanosine is pancreatitis and occurs in both adults and children. Patients receiving doses >360 mg/m^2 have a greater risk of developing pancreatitis. Seven of 60 patients receiving didanosine at a dose of greater than 360 mg/m^2 developed pancreatitis whereas none of 35 patients who received less than 270 mg/m^2/day developed pancreatitis. The effect of didanosine on the pancreas varies, ranging from mild hyperamylasaemia without abdominal pain to severe fulminant pancreatitis with pseudocyst formation, pancreatic necrosis and severe metabolic derangements including hyperosmolar non-ketotic diabetic syndrome and hypertriglyceridaemia.[46,47] There is a strong correlation between abnormal transaminase levels prior to treatment with didanosine and the subsequent development of pancreatitis. Patients with haemophilia who have HIV are at particular risk of pancreatitis if treated with didanosine. In this group of patients pancreatitis resolved when therapy was interrupted but recurred in two of four rechallenged patients.[47] There is at least one reported case of acute fatal pancreatitis in a child secondary to didanosine.[48]

Symptoms such as nausea, vomiting and abdominal pain with a concomitant rise in liver enzyme levels are the hallmarks of didanosine-induced pancreatitis. Asymptomatic hyperamylasaemia was not related to the development of didanosine-induced pancreatitis. Additionally hyperamylasaemia is not predictive of the later development of pancreatitis if seen prior to onset of treatment with didanosine. Therefore, it is unlikely that intermittent measurement of pancreatic enzymes would be useful as a monitoring tool.

Didanosine causes hepatotoxicity ranging from steatosis to fulminant hepatitis, and lactic acidosis.[41,42,46] Abnormal liver function tests prior to the use of didanosine is associated with an increased risk of hepatotoxicity during treatment. The adverse effects of the drug tend to be reversible and didanosine can often be reinstated at a lower dose with improved tolerance. Phase I trials of didanosine showed that asymptomatic elevation of transaminase levels, that is up to five times the upper limit of normal, occurred in 25% of patients.[49] Among 34 children enrolled in a trial by Lacaille et al.,[46] six patients with normal liver function tests at entry developed liver abnormalities, two of these six died of fulminant hepatic failure. The children who died secondary to liver failure may have had a concurrent viral infection, as one had proven adenovirus infection. Patients receiving didanosine seem to be more sensitive to

viral aggression because of some unknown effect of the drug on hepatic metabolism.[46]

In a study by Mueller et al.,[41] 11 of 103 patients had didanosine therapy discontinued secondary to toxicities; another 18 patients required dosing modifications. Haemoglobin levels below 9.5 g/dl were found in 18% of patients and didanosine was discontinued secondary to persistent or recurrent anaemia in three patients with haemoglobin levels less than 8 g/dl. However, all of these patients had other contributing factors to their anaemia. Neutropenia was evident in 6 of 103 patients. The rate of these haematological toxicities is much lower than with zidovudine therapy.[41,42]

Whitcup et al.,[50] documented 3 of 43 (7%) children receiving didanosine who developed peripheral atrophy of the retinal pigment epithelium. All three children had normal eye examinations before starting treatment. None of the three patients had any loss of visual acuity (all three had 6/6 vision) and one patient had constriction of visual fields on Goldman perimetry. The retinal atrophic lesions tended to occur in children receiving doses >360 mg/m^2/day. Progression of retinal atrophy continued even at low doses of didanosine but stopped after treatment was discontinued. Retinal lesions were first observed after 36 weeks of treatment. The lesions were generally located in the mid-periphery of the fundus. Another child out of 95 children studied[51] developed a retinal lesion at a dosage of only 270 mg/m^2/day. Regular direct ophthalmoscopy is warranted in patients treated with didanosine, especially when presenting with visual disturbances.

There have not as yet been any case reports of the neurotoxic properties of didanosine in children, although mania reported in adults may represent an immunological reaction to didanosine in the brain.[52] Peripheral neuropathy seen in adults while receiving didanosine appears to be rare in children, occurring in less than 3% of patients.[43,44]

Blanche et al., [45] describe a cohort of 34 children, one of whom refused to take didanosine because of the taste while five had accelerated intestinal transit time during treatment including gastrointestinal irritability. Nausea, vomiting, diarrhoea and/or abdominal pain have been reported in adults and children receiving didanosine either in combination with other nucleoside analogues or as monotherapy. Some of the less serious adverse effects of didanosine seen in adults but not as yet reported in children included hypokalaemia and headache.[53] Asymptomatic persistent elevation of uric acid levels was seen in 7 of 103 children.

Didanosine has been used in combination with several other nucleoside reverse transcriptase inhibitors including stavudine and zidovudine and has been well tolerated. There was no increased rate of toxicities compared with stavudine, zidovudine or didanosine monotherapy.[54]

1.2.3 Zalcitabine

In children, there is considerable interpatient variability of zalcitabine (dideoxycytidine) absorption following oral administration. The syrup formulation of zalcitabine is a raspberry-flavoured solution with a concentration of 0.1 mg/ml. Zalcitabine has a serum half life of 0.8–1.4 hours.[55] Zalcitabine has a lower bioavailability and half-life in children when compared with adults. This seems to be due to the more rapid clearance in children rather than to decreased oral absorption. Zalcitabine is cleared mainly by the kidneys with 75% of the parent drug recovered in urine.[28,56] Zalcitabine penetrates the CSF poorly and children who received zalcitabine monotherapy in early studies had a deterioration of their CNS disease.[4,57]

Zalcitabine is phosphorylated to the active triphosphate form intracellularly. Once phosphorylated zalcitabine blocks viral DNA synthesis by inhibiting reverse transcriptase and inhibiting DNA synthesis via its affinity to the host polymerase, especially polymerase-β and -γ which are responsible for DNA repair and mitochondrial DNA generation. This is thought to account for the observed toxicities of zalcitabine.[8] Zalcitabine has a very narrow therapeutic index.

In adult studies, up to 31% of patients in some clinical trials developed a peripheral sensori-motor neuropathy.[53] This neuropathy usually manifests itself as a dysaesthesia of the soles of the feet and may progress to severe pain requiring narcotic pain relief. The neuropathy is dose related and is reversible over some weeks when zalcitabine is discontinued. The incidence of peripheral neuropathy reported in adult studies has not been replicated in studies of children. Bakshi et al.[56] found only 2 of 127 children developed reversible peripheral neuropathy. This is due to children having received lower doses (and having better clearance) of zalcitabine than adults as the peripheral neuropathy is a dose related effect. Spector et al.,[58] studied two dose levels of zalcitabine in zidovudine-experienced children, peripheral neuropathy occurred at a rate of approximately 5% at both dosage levels.

A European randomised, double-blind, controlled trial study published in 1996 compared the combination of zidovudine plus didanosine or zalcitabine with zidovudine monotherapy.[59] The arm with zalcitabine showed an increased incidence of peripheral neuropathy and painful mouth ulcers. The incidence of nausea and vomiting was higher in the zalcitabine group and the drug was less palatable. While the group studied included mainly adults there were a number of adolescents included in the study.

When zidovudine plus zalcitabine was compared with zidovudine monotherapy, there was an increase in level 3 and 4 haematological toxicities in the combination therapy group. This is largely due to the more frequent development of neutropenia in those receiving combination therapy. Eighteen of 127 (13%) patients receiving zalcitabine plus zidovudine developed neutropenia of less than 400 cells/mm^3 while only 5 of 123 (5%) did in the monotherapy arm.

1.2.4 Abacavir

Abacavir is a nucleoside analogue reverse transcriptase inhibitor. It is converted into its active form intracellularly by phosphorylation to carbovir triphosphate. Abacavir is available as abacavir sulphate liquid at a concentration of 10 mg/ml. Abacavir has a half-life of approximately 1.2–3 hours and penetrates well into the CSF.[60] There is a high degree of pharmacokinetic variability in paediatric patients.[61] The recommended paediatric dosage is now 8 mg/kg after a study comparing a 4 and 8 mg/kg dosage on a twice daily basis.[62] This is approximately double the adult recommended dosage on a milligram per kilogram basis. Abacavir undergoes extensive hepatic metabolism in humans with less than 2% of the drug appearing unchanged in the urine. The major metabolites of abacavir are then excreted in the urine. Eighteen HIV-infected infants and children who received liquid abacavir in a phase I single dose study did not experience any serious adverse events.[60,62]

Abacavir has been observed to cause hypersensitivity reactions in approximately 3% of adults studied, usually between weeks 1 and 4 of treatment.[63] Permanent discontinuation of the drug is necessary as reintroduction may lead to a life-threatening hypersensitivity reaction. In a phase III trial, 4 of 146 children treated with abacavir in combination with zidovudine and lamivudine manifested a hypersensitivity reaction to the drug.[64] Abacavir hypersensitivity reaction usually presents with fever, rash malaise and fatigue with some gastrointestinal symptoms such as nausea, vomiting and diarrhoea. Respiratory symptoms including dyspnoea, cough and pharyngitis may occur in a minority of cases. The presentation of this reaction can make it difficult to distinguish from acute infections. Most cases of hypersensitivity occur within 6 weeks of commencement of therapy. Rechallenge with abacavir may cause reappearance of symptoms within hours and may be fatal.[65,66]

Nausea, vomiting, malaise and fatigue were minor adverse events that have been reported in adult and adolescent patients. The incidence of nausea appears to be dose related. In a non randomised expanded access study of 154 children, the most frequently reported adverse effects were nausea and diarrhoea (50%) and fever and chills (25%).[61]

2. Non-Nucleoside Reverse Transcriptase Inhibitors

2.1 Nevirapine

Nevirapine is a benzodiazepine derivative and a potent inhibitor of reverse transcriptase activity. It is rapidly absorbed after oral administration with a long-terminal half-life (>24 hours).[3,8] The half life of nevirapine in infants is increased compared with that observed following administration of single doses in older children. Its elimination is prolonged in both pregnant mothers and infants.[67] Nevirapine is rapidly absorbed from the gastrointestinal tract with a bioavailability of 90%. It may be administered without regard to food. Plasma protein binding is about 60%. Nevirapine has synergistic activity with zidovudine.[8] Nevirapine crosses the placenta and is also found in breast milk. It is metabolised by the CYP3A system. The metabolites undergo further glucuronide conjugation and are then excreted by the kidney with only a small proportion eliminated by the kidney as unchanged drug. It is a mild to moderate inducer of the hepatic CYP system, including autoinduction of its own metabolism. In studies of rabbits and rats, no teratogenicity was observed.[68]

Initial phase I monotherapy trials found that nevirapine was well tolerated with only 1 of 21 children developing a rash.[69] Eight infants born to seven mothers infected with HIV were studied. No adverse effects were observed in mothers or children.[67] In a study by Musoke et al.,[70] 21 HIV-infected women and their infants experienced no adverse events.

In one trial of nevirapine in children, the most common adverse events were rash (in 24%), granulocytopenia (16%), vomiting (14%), fatigue (11%), nausea (11%) and dizziness, headache, nervousness, and somnolence (8% each). Elevation in liver function tests is another adverse event described with nevirapine therapy. In two later trials the rate of adverse effects was between 6.9 and 8.1%. Most withdrawals from the trial were due to nevirapine-related adverse events including rash, fever, neutropenia and circumoral and periorbital oedema.[71]

The serious life-threatening drug eruption (Stevens-Johnson syndrome) has occurred in adults taking nevirapine with an incidence of 0.3%.[72] Rash occurs at a slightly higher rate in children than in adults and is the most common adverse event reported in children. This rash usually develops within the first 6 weeks of therapy.

2.2 Delavirdine

Delavirdine is rapidly absorbed from the gastrointestinal tract and has a bioavailability of >80%. It may be administered on an empty stomach and is 98% plasma protein bound. It achieves poor CSF concentrations. Delavirdine is metabolised by the CYP system, mainly the CYP3A enzyme system, to several inactive metabolites. Elimination is through the faeces and urine (44 and 51%, respectively). Less than 5% is excreted in urine as unchanged drug. Its plasma half-life is 5.8 hours. Delavirdine inhibits the CYP activity including its own metabolism.[68] In adults, rash is the most common adverse effect. Other toxicities include headache, fatigue, vomiting and diarrhoea. Laboratory abnormalities such as increased transaminase levels have been reported. Increase in the incidence of ventricular septal defects (VSD) and infant mortality was noted when the drug was administered to pregnant rats. Ectopic pregnancies and VSD have been reported in humans taking delavirdine.[68]

2.3 Efavirenz

Efavirenz is the newest of the non-nucleoside reverse transcriptase inhibitors. It is 99.5–99.8% bound to plasma proteins. It is poorly absorbed into CSF. Efavirenz should not be taken with high fat meals because of the resultant increase in the absorption of efavirenz and therefore variable bioavailability. Efavirenz is metabolised by the CYP system, notably CYP3A4, to inactive hydroxylated metabolites which undergo glucuronide conjugation and are subsequently eliminated by the kidneys. It also induces CYP enzymes including

its own metabolism. Its plasma half life is 40–55 hours in adults.[68] Efavirenz is formulated in moderately sized capsules and can be difficult for children to tolerate leading to problems with compliance.[73] Fetal brain malformations have been noted in primates exposed to efavirenz, and the drug therefore should be avoided in pregnant women.

In a study involving combination therapy with efavirenz and nelfinavir, and nucleoside analogue reverse transcriptase inhibitors in children, Starr et al.[73] reported that about 30% of children had moderately severe rash similar to that seen with efavirenz therapy in HIV-infected adults, occurring typically within the first 2 weeks of treatment. Nine percent discontinued treatment permanently as a result. Eight of 57 (14%) children had mild dizziness or light headedness that resolved once efavirenz was administered at bed time rather than in the morning.[73]

3. Protease Inhibitors

3.1 Ritonavir

Ritonavir is a potent antiretroviral protease inhibitor. As with other protease inhibitors, ritonavir should be given with protein- or fat-containing food or drink. Ritonavir can be given as capsules or in liquid form.[74] The liquid formulation of ritonavir has an oily consistency and an unpleasant, bitter, long-lasting taste.[75] It contains 43% ethanol and care should be taken when given in combination with disulfiram drugs (e.g. metronidazole).[76] Ritonavir has an oral bioavailability of 75% and a plasma half-life of 3–5 hours. Plasma protein binding is 98–99%. The main route of excretion of the drug is in the faeces (>80%). Less than 5% of the dose is excreted unchanged in the urine. Ritonavir induces its own metabolism (autoinduction) and a steady state is reached after 2 weeks of treatment. Plasma concentrations of ritonavir are not correlated with toxicity. Ritonavir is extensively metabolised by CYP enzymes in the liver.

Ritonavir is the most potent and broadest inhibitor of the CYP3A4 enzyme system of the protease inhibitors. Drugs using the same metabolic pathway including azole antifungals and macrolides are likely to be given to patients affected with HIV and ritonavir influences their pharmacokinetics.[68,77] The combination of ritonavir and indinavir causes inhibition of the CYP system by both drugs. This allows reduced doses of each drug to be used to achieve serum concentrations similar to those obtained when each drug is used alone.[78]

Mueller et al.[76] found that nausea, burping, diarrhoea and abdominal pain were experienced by almost all children studied. These symptoms, however, usually subsided within 2–8 weeks of starting ritonavir monotherapy.[76] Fourteen percent of children withdrew from the study because of gastrointestinal toxicity, and of these more than half had intolerable nausea and vomiting despite dose reduction. Nine patients complained of anorexia, although 14 reported an increase in appetite. These symptoms were compounded by the addition of zidovudine and didanosine. In a more recent study of ritonavir, gastrointestinal symptoms were limited by using preventative antiemetic medication. In a recent study of 24 children using this method only two discontinued ritonavir therapy secondary to severe gastrointestinal toxicity.[74]

Ritonavir is hypothesised to cause liver toxicity. A recent study described 4 of 48 children with hepatic transaminase levels greater than five times the upper limit of normal.[76] These patients had a prior history of intermittently raised hepatic enzyme levels. These potential liver toxicities suggest care should be taken in children with pre-existing liver function abnormalities. Thuret et al.[74] reported one of 22 patients had a grade 3 elevation of transaminase levels. In a study by Rutstein et al.[79] two of nine children studied developed severe elevation of hepatic transaminase levels requiring discontinuation of therapy.

Increase in mean serum triglyceride levels and cholesterol levels was an expected toxicity of ritonavir therapy.[80] Mean increase in cholesterol level has been documented, patients with complete

antiviral response having a significantly higher cholesterol level than patients with no response.[77] This raises the concern that elevation in plasma levels of triglyceride and cholesterols may cause a theoretical increase in the risk of pancreatitis in patients already predisposed to this as a result of HIV infection itself or due to other antiretroviral medications.[80]

There have been at least four cases reported to the US FDA of children developing a cushingoid appearance, two of whom had associated hypertension following treatment with ritonavir. At least one of these patients had ritonavir discontinued with resolution of symptoms.[25] Minor adverse events noted in children include circumoral paraesthesia and headaches (in up to 31% of children studied).[76]

There have been reports of multiple cases of spontaneous bleeding episodes in patients with haemophilia being treated with protease inhibitors, especially ritonavir.[81] There has been at least one case report of a teenager who had an increase in spontaneous active bleeding episodes.[81]

3.2 Saquinavir

Saquinavir is generally poorly absorbed in adults and children. Absorption is increased with food, and it therefore should be taken with a high fat meal.[68] It is metabolised by the CYP isoenzyme CYP3A4 to an active compound that is excreted by the kidney. It is also a weak inhibitor of the CYP3A4 system. It is 98% plasma protein bound. Saquinavir comes in hard and soft gel capsule formulations. The soft gel capsule is more bioavailable. The newer soft gel capsule preparation is under study in children and initial pharmokinetic study results are similar to those seen in adults. Saquinavir has a half-life of approximately 13 hours. As saquinavir inhibits the CYP system, it can be used in combination with other protease inhibitors to increase the serum concentration of the second drug allowing longer dosage intervals.

In adult studies, diarrhoea was the most common single adverse event, occurring in 4% of patients. Nausea, abdominal discomfort and reversible elevations in liver function tests are other common gastrointestinal adverse effects. There was also a very low incidence of headache, paraesthesia, asthenia, skin rash and musculoskeletal pain. There is little paediatric experience with saquinavir at the present time.

3.3 Indinavir

Indinavir is delivered in several forms including free-base liquid suspension, and 200 and 400mg capsules. Indinavir is rapidly absorbed after administration of suspension and capsule formulations in the fasting state with a serum half-life of approximately 0.9 hours. Bioavailability of the suspension is substantially lower than that of the sulphate salt capsules. It is associated with extensive inter-patient variability and is not currently readily available in this form.[82] The capsules can be opened and dissolved in 5–10ml of water.[68] This substance has a bitter taste and leads to problems of adherence in young children.[83] In one study, 25% of patients had to be changed to nelfinavir due to poor palatability.[83] Indinavir needs to be taken 1 hour before or 2 hours after meals. If given with a high fat, high protein meal, absorption is reduced and peak plasma concentration decreases by 80%.[68] Plasma protein binding is 60%.

Children in general have a higher than expected peak serum exposure when compared with adults (of the same dose/m^2) which may contribute to the higher efficacy and higher risk of renal toxicity when compared with adult studies.[84] However, trough concentrations on normal 8 hourly dosage regimens (as in adults) may be too low (<0.1 mg/L) inviting virological resistance. This suggests that 6-hourly administration (at a lower dosage) may in fact be a preferable regimen.[85] Indinavir is 80% metabolised in the liver via the CYP enzyme system and is an inhibitor of the CYP3A4 hepatic enzyme system. Most of the drug is excreted in the bile, a small amount of unchanged drug (20%) and its metabolites are excreted in the urine.[86]

Mueller et al.[82] found that 13% of patients had haematuria during the first 6 months of treatment.

One of 54 patients passed a kidney stone and all seven patients who had haematuria had unidentified crystals in their urine. The episodes of haematuria resolved with adequate hydration and without impairment of renal function. Increasing doses of indinavir resulted in an increased number of children with haematuria and nephrolithiasis. In a study by Gatti et al.,[84] 5 of 11 children had at least one episode of renal adverse effects over a 12-month period (45.5%). These toxicities included flank or abdominal pain, renal colic, macrohaematuria, kidney stones and mild transient increases in serum creatinine levels. A patient developed renal failure which resolved 3 months post-withdrawal of indinavir.[84] Indinavir has also been reported to cause a tubulo-interstitial nephritis.[86] Indinavir precipitates in the kidney as it is poorly soluble at a pH lower than 5.0. Low urine pH can thus lead to formation of uric acid or calcium calculi. Pure indinavir stones tend to be radiolucent on plain x-ray although they may form the nidus of a mixed stone rendering them radio opaque. The ability to increase oral fluids prior to administration of indinavir is important when considering a child's tolerance to this medication. Rutstein et al.,[79] reported that 5 of 18 children receiving indinavir developed nephrolithiasis with two developing interstitial nephritis.[79]

Unconjugated hyperbilirubinaemia and increase in alkaline phosphatase levels without an increase in transaminase levels is associated with indinavir therapy and can occur in up to 10% of patients at higher doses.[8] Mild gastrointestinal complaints including nausea and vomiting have been reported during indinavir therapy with one patient requiring cessation of treatment due to intractable vomiting.[84]

Rash secondary to indinavir therapy tends to occur within two weeks of initiation of therapy (in the majority of patients). The rash is localised initially and subsequently spreads and is associated with pruritus.[87]

Abnormal body fat distribution or lipodystrophy has been reported in multiple articles in HIV-1 infected adults treated with protease inhibitors. This abnormal body fat distribution is increasingly being noted in children as duration of exposure to the drug increases.[88] Commonly, the abnormal fat distribution has been noticed in the abdomen, upper back and face.

There is a report of an adolescent receiving indinavir combination therapy developing platelet dysfunction. This HIV-1 infected patient with haemophilia had at least one episode of prolonged bleeding secondary to this toxicity. There have been multiple reports in the adult literature of HIV-infected patients with haemophilia with an increased bleeding tendency following the administration of protease inhibitors including indinavir. This resulted in an increased occurrence of spontaneous haematomas.[89,90]

Paronychia and ingrown toenails have been a commonly reported adverse effect of any protease inhibitors in adults. There has been at least one case report of this occurring in children.[91] In this case the paronychia was associated with pyogenic granuloma.

3.4 Nelfinavir

Nelfinavir is a selective HIV protease inhibitor.[92] Nelfinavir is extensively protein bound (98%) and is metabolised by at least four hepatic CYP isoenzymes. It has two active metabolites, one with equivalent anti-HIV activity and the other with 10–20% of the activity of the parent compound. Clearance of nelfinavir is greater in children than in adults and the serum half-life in children is approximately 1 ± 0.5 hours.[92,93] Children thus require doses 2–3 times higher than adults to achieve similar concentrations.

Nelfinavir is supplied as 250mg tablets and as an oral powder at a dose of 50mg of nelfinavir per gram which can be administered with milk, infant formula or water.[93] Powder and tablet formulations produce similar *in vitro* concentrations in children. The powder has a bitter taste and for this reason the tablet dissolved in water may be more tolerable than the powder. Nelfinavir powder contains 11.2mg of phenylalanine per gram and should be used with caution in patients with phenylketo-

nuria.[92] Nelfinavir is taken with food in order to optimise absorption of the drug. Nelfinavir administration has not been associated with fetal abnormalities in animals. There is limited data on human use during pregnancy and the drug therefore is designated a pregnancy category B drug by the US FDA (table I)[92] and B3 in Australia (table II).

Krogstad et al.[93] studied 62 patients receiving nelfinavir in combination with reverse transcriptase inhibitors and five experienced mild adverse effects including fever, sweating, back pain, abdominal pain, anorexia, nausea and vomiting. Mild transient diarrhoea was a relatively common adverse effect occurring in 14 children (22%). The diarrhoea was generally reported within 1–2 weeks of commencing nelfinavir treatment. Four of 62 patients developed a rash. Laboratory changes included anaemia, neutropenia, thrombocytopenia, hypoglycaemia, increased serum creatinine levels, hyperamylasaemia, hypercalaemia and elevated transaminase levels. These were all transient and could not be attributed solely to nelfinavir.

In a study by Starr et al.[73] of nelfinavir use in combination with efavirenz and nucleoside reverse transcriptase inhibitors, diarrhoea reported in 18% was thought to be secondary to nelfinavir. Dizziness was another reported adverse event although this was attributed to efavirenz by the authors. However, subsequent studies have reported the association of nelfinavir with dizziness.[94] Funk et al.[95] reported that 8 of 16 patients receiving nelfinavir treatment had elevated serum triglyceride levels, while five had elevated cholesterol levels. Nelfinavir can be given in two instead of three doses per day thereby facilitating adherence to this medication.[95]

In a Spanish study, 10 of 42 children treated with nelfinavir (with reverse transcriptase inhibitors) presented with rash.[96] The rash tended to be erythematous with generalised maculopapules involving the face, trunk, palms and soles. The rash was generally self limiting (lasting 5–7 days). Nelfinavir therapy was not discontinued, and no ongoing adverse events occurred.

There is at least one case report in the literature of visceral obesity, hypertriglyceridaemia and hypercortisolism in a 9-year-old boy being treated with nelfinavir.[97] He demonstrated the classical lipodystrophy habitus with increased truncal fat, decreased arm and leg fat, with a marked increase in visceral adipose tissue. Fasting triglyceride levels were increased and total cholesterol levels were normal. In adults, this syndrome has been described with peripheral fat wasting, truncal fat accumulation, hyperlipidaemia and insulin resistance. This is thought to be secondary to protease inhibitors partly inhibiting formation of proteins involved in lipid metabolism.

3.5 Lopinavir/Ritonavir

A combination formulation of lopinavir and ritonavir has recently been developed for clinical use. Lopinavir is a protease inhibitor that is rapidly metabolised by the hepatic CYP system *in vitro*. Co-administration of lopinavir with ritonavir inhibits its metabolism, thereby significantly increasing lopinavir plasma concentration. At the doses contained in the formulation ritonavir acts only as a pharmacokinetic enhancer, not as an antiretroviral agent. The lopinavir-ritonavir combination is available as capsules of lopinavir 133.3mg and ritonavir 33.3mg and as a paediatric oral solution containing lopinavir 80mg and ritonavir 20mg per ml and is given at 12 hourly intervals. The lopinavir-ritonavir combination should be taken with food. Recommended paediatric doses are calculated on weight (mg/kg) and whether or not nevirapine or efavirenz (both of which induce lopinavir metabolism) is being concomitantly administrated. There is insufficient data to recommend dosage adjustment in heavily antiretroviral therapy pre-treated children.[98]

Clinical experience with the lopinavir-ritonavir combination in children is limited. One phase I/II study (ABT study M98-940) involving 100 HIV-infected children aged between 6 months and 12 years followed the children for 60 weeks.[99] The lopinavir-ritonavir combination was well tolerated with only one child discontinuing therapy due to

an adverse event (pancreatitis). Other adverse events were similarly uncommon in this group and included rash (2%) and gastrointestinal disturbance (4%). Grade 3/4 laboratory abnormalities included hyperamylasaemia (6%), thrombocytopenia (4%), hypo- and hypernatraemia (3% each) and transaminase level elevations (3%).

4. Conclusion

In conclusion, adverse events have been described with all the classes of antiretrovirals used in children. However, overall, antiretrovirals are well tolerated in children, and adverse events are rarely life threatening. Most adverse events resolve with discontinuation of the drug (with or without reintroduction). The most common adverse effects appear to be haematological in the nucleoside reverse transcriptase inhibitors, with mitochondrial toxicity being a rare event. Dermatological complications are seen mainly with non-nucleoside reverse transcriptase inhibitors, and gastrointestinal intolerance is most frequently associated with the protease inhibitors. Unusual complications of long-term protease inhibitor therapy have been documented in children but appear to be less frequent than in adults. Overlapping drug toxicities and drug-drug interactions remain a challenge. Simpler, more effective therapeutic regimens in the future may contribute to a decreasing incidence of adverse events.

Acknowledgements

No sources of funding were used to assist in the preparation of this manuscript. The authors have no conflicts of interest that are directly relevant to the contents of this manuscript.

The authors acknowledge the help of Christine Monie and Jessica Clark for their help with the literature search and Susan Swan for her typing skills.

References

1. Epidemiological Slide Set [online]. Available from URL: http://www.unaids.org/barcelona/presskit/epigraphics/epicore_june2002.htm [Accessed 2002 Aug 22]
2. de Martino M, Tovo PA, Balducci M, et al. Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. Italian Register for HIV Infection in Children and the Italian National AIDS Registry. JAMA 2000; 284: 190-7
3. Mueller BU. Antiviral chemotherapy. Curr Opin Pediatr 1997; 9: 178-83
4. Pizzo PA, Wilfert C. Antiretroviral therapy for infection due to human immunodeficiency virus in children. Clin Infect Dis 1994; 19 (1): 177-96
5. Shepp DH, Ramirez-Ronda C, Dall L, et al. A comparative trial of zidovudine administered every four versus every twelve hours for the treatment of advanced HIV disease. J Acquir Immune Defic Syndr Hum Retrovirol 1997; 15: 283-8
6. Stretcher BN, Pesce AJ, Murray JA, et al. Concentrations of phosphorylated zidovudine (ZDV) in patient leukocytes do not correlate with ZDV dose or plasma concentrations. Ther Drug Monit 1991; 13: 325-31
7. Olivero OA, Anderson LM, Diwan BA, et al. Transplacental effects of 3′-azido-2′,3′-dideoxythymidine (AZT): tumorigenicity in mice and genotoxicity in mice and monkeys. J Natl Cancer Inst 1997; 89: 1602-8
8. Mueller BU, Kline MW, Pizzo PA. Antiretroviral treatment. In: Pizzo PA, Wilfert CM, editors. Pediatric AIDS: the challenge of HIV infection in infants, children and adolescents. 3rd ed. Baltimore (MA): William & Wilkins, 1998: 463-86
9. Newell ML, Gibb DM. A risk-benefit assessment of zidovudine in the prevention of perinatal HIV transmission. Drug Saf 1995; 12 (4): 274-82
10. McKinney Jr RE, Maha MA, Connor EM, et al. A multicenter trial of oral zidovudine in children with advanced human immunodeficiency virus disease. The Protocol 043 Study Group. N Engl J Med 1991; 324: 1018-25
11. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Department of Health and Human Services and the Henry J. Kaiser Family Foundation. Ann Intern Med 1998; 128 (12 Pt 2): 1079-100
12. McKinney Jr RE, Pizzo PA, Scott GB, et al. Safety and tolerance of intermittent intravenous and oral zidovudine therapy in human immunodeficiency virus-infected pediatric patients. Pediatric Zidovudine Phase I Study Group. J Pediatr 1990; 116 (4): 640-7
13. Pizzo PA. Treatment of human immunodeficiency virus-infected infants and young children with dideoxynucleosides. Am J Med 1990; 88 (5B): 16S-19S
14. Brady MT, McGrath N, Brouwers P, et al. Randomized study of the tolerance and efficacy of high- versus low-dose zidovudine in human immunodeficiency virus-infected children with mild to moderate symptoms (AIDS Clinical Trials Group 128). Pediatric AIDS Clinical Trials Group. J Infect Dis 1996; 173 (5): 1097-106
15. Palasanthiran P, Ziegler JB, Kemp AS, et al. Zidovudine (AZT) therapy in children with HIV infection: the Australian experience. J Paediatr Child Health 1990; 26 (5): 257-62
16. Bozzette SA, Forthal D, Sattler FR, et al. The tolerance for zidovudine plus thrice weekly or daily trimethoprim-sulfamethoxazole with and without leucovorin for primary prophylaxis in advanced HIV disease. California Collaborative Treatment Group. Am J Med 1995; 98 (2): 177-82
17. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med 1994; 331: 1173-80
18. Walter EB, Drucker RP, McKinney RE, et al. Myopathy in human immunodeficiency virus-infected children receiving

long-term zidovudine therapy. J Pediatr 1991; 119 (1 Pt 1): 152-5
19. Lipshultz SE, Orav EJ, Sanders SP, et al. Cardiac structure and function in children with human immunodeficiency virus infection treated with zidovudine. N Engl J Med 1992; 327 (18): 1260-5
20. Domanski MJ, Sloas MM, Follmann DA, et al. Effect of zidovudine and didanosine treatment on heart function in children infected with human immunodeficiency virus. J Pediatr 1995; 127 (1): 137-46
21. McKinney Jr RE. Antiviral therapy for human immunodeficiency virus infection in children. Pediatr Clin North Am 1991; 38 (1): 133-51
22. Steinherz LJ. Cardiomyopathy related to acquired immunodeficiency syndrome in children [letter; comment]. J Pediatr 1996; 128 (5 Pt 1): 721
23. Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. Lancet 1999; 354 (9184): 1084-9
24. Scalfaro P, Chesaux JJ, Buchwalder PA, et al. Severe transient neonatal lactic acidosis during prophylactic zidovudine treatment. Intensive Care Med 1998; 24 (3): 247-50
25. Mann M, Piazza-Hepp T, Koller E, et al. Unusual distributions of body fat in AIDS patients: a review of adverse events reported to the Food and Drug Administration. AIDS Patient Care STDS 1999; 13 (5): 287-95
26. Balis FM, Pizzo PA, Eddy J, et al. Pharmacokinetics of zidovudine administered intravenously and orally in children with human immunodeficiency virus infection. J Pediatr 1989; 114: 880-4
27. Balis FM, Pizzo PA, Murphy RF, et al. The pharmacokinetics of zidovudine administered by continuous infusion in children. Ann Intern Med 1989; 110: 279-85
28. Yarchoan R, Mitsuya H, Myers CE, et al. Clinical pharmacology of 3′-azido-2′,3′-dideoxythymidine (zidovudine) and related dideoxynucleosides [published erratum appears in N Engl J Med 1990 Jan 25; 322 (4): 280]. N Engl J Med 1989; 321: 726-38
29. Tosti A, Gaddoni G, Fanti PA, et al. Longitudinal melanonychia induced by 3′-azidodeoxythymidine: report of 9 cases. Dermatologica 1990; 180: 217-20
30. Russo F, Collantes C, Guerrero J. Severe paronychia due to zidovudine-induced neutropenia in a neonate. J Am Acad Dermatol 1999; 40 (2 Pt 2): 322-4
31. Kline MW, Van Dyke RB, Lindsey JC, et al. A randomized comparative trial of stavudine (d4T) versus zidovudine (ZDV, AZT) in children with human immunodeficiency virus infection. AIDS Clinical Trials Group 240 Team. Pediatrics 1998; 101 (2): 214-20
32. Merrill DP, Moonis M, Chou TC, et al. Lamivudine or stavudine in two- and three-drug combinations against human immunodeficiency virus type 1 replication *in vitro*. J Infect Dis 1996; 173: 355-64
33. Kline MW, Dunkle LM, Church JA, et al. A phase I/II evaluation of stavudine (d4T) in children with human immunodeficiency virus infection. Pediatrics 1995; 96: 247-52
34. Browne MJ, Mayer KH, Chafee SB, et al. 2′,3′-didehydro-3′-deoxythymidine (d4T) in patients with AIDS or AIDS-related complex: a phase I trial. J Infect Dis 1993; 167: 21-9
35. Miller KD, Cameron M, Wood LV, et al. Lactic acidosis and hepatic steatosis associated with use of stavudine: report of four cases. Ann Intern Med 2000; 133 (3): 192-6
36. Moore KH, Shaw S, Laurent AL, et al. Lamivudine/zidovudine as a combined formulation tablet: bioequivalence compared with lamivudine and zidovudine administered concurrently and the effect of food on absorption. J Clin Pharmacol 1999; 39 (6): 593-605
37. Johnson MA, Moore KH, Yuen GJ, et al. Clinical pharmacokinetics of lamivudine [review]. Clin Pharmacokinet 1999; 36 (1): 41-66
38. Lewis LL, Venzon D, Church J, et al. Lamivudine in children with human immunodeficiency virus infection: a phase I/II study. The National Cancer Institute Pediatric Branch – Human Immunodeficiency Virus Working Group. J Infect Dis 1996; 174 (1): 16-25
39. Sokal EM, Roberts EA, Mieli-Vergani G, et al. A dose ranging study of the pharmacokinetics, safety, and preliminary efficacy of lamivudine in children and adolescents with chronic hepatitis B. Antimicrob Agents Chemother 2000; 44 (3): 590-7
40. Horneff G, Adams O, Wahn V. Pilot study of zidovudine-lamivudine combination therapy in vertically HIV-infected antiretroviral-naive children. AIDS 1998; 12 (5): 489-94
41. Mueller BU, Butler KM, Stocker VL, et al. Clinical and pharmacokinetic evaluation of long-term therapy with didanosine in children with HIV infection. Pediatrics 1994; 94 (5): 724-31
42. Perry CM, Noble S. Didanosine: an updated review of its use in HIV infection [review]. Drugs 1999; 58 (6): 1099-135
43. Balis FM, Pizzo PA, Butler KM, et al. Clinical pharmacology of 2′,3′-dideoxyinosine in human immunodeficiency virus-infected children. J Infect Dis 1992; 165: 99-104
44. Butler KM, Husson RN, Balis FM, et al. Dideoxyinosine in children with symptomatic human immunodeficiency virus infection. N Engl J Med 1991; 324: 137-44
45. Blanche S, Calvez T, Rouzioux C, et al. Randomized study of two doses of didanosine in children infected with human immunodeficiency virus. J Pediatr 1993; 122: 966-73
46. Levin TL, Berdon WE, Tang HB, et al. Dideoxyinosine-induced pancreatitis in human immunodeficiency virus-infected children. Pediatr Radiol 1997; 27 (2): 189-91
47. Butler KM, Venzon D, Henry N, et al. Pancreatitis in human immunodeficiency virus-infected children receiving dideoxyinosine. Pediatrics 1993; 91 (4): 747-51
48. Kahn E, Anderson VM, Greco MA, et al. Pancreatic disorders in pediatric acquired immune deficiency syndrome. Hum Pathol 1995; 26 (7): 765-70
49. Lacaille F, Ortigao MB, Debre M, et al. Hepatic toxicity associated with 2'-3' dideoxyinosine in children with AIDS. J Pediatr Gastroenterol Nutr 1995; 20 (3): 287-90
50. Whitcup SM, Butler KM, Caruso R, et al. Retinal toxicity in human immunodeficiency virus-infected children treated with 2′,3′-dideoxyinosine. Am J Ophthalmol 1992; 113 (1): 1-7
51. Whitcup SM, Butler KM, Pizzo PA, et al. Retinal lesions in children treated with dideoxyinosine. N Engl J Med 1992; 326 (18): 1226-7
52. Brouillette MJ, Chouinard G, Lalonde R. Didanosine-induced mania in HIV infection [letter; comment]. Am J Psychiatry 1994; 151 (12): 1839-40
53. Lipsky JJ. Zalcitabine and didanosine [review]. Lancet 1993; 341 (8836): 30-2
54. Kline MW, Van Dyke RB, Lindsey JC, et al. Combination therapy with stavudine (d4T) plus didanosine (ddI) in children with human immunodeficiency virus infection. The Pediatric AIDS Clinical Trials Group 327 Team. Pediatrics 1999; 103 (5): e62
55. Chadwick EG, Nazareno LA, Nieuwenhuis TJ, et al. Phase I evaluation of zalcitabine administered to human immuno-

deficiency virus-infected children. J Infect Dis 1995; 172: 1475-9
56. Bakshi SS, Britto P, Capparelli E, et al. Evaluation of pharmacokinetics, safety, tolerance, and activity of combination of zalcitabine and zidovudine in stable, zidovudine-treated pediatric patients with human immunodeficiency virus infection. AIDS Clinical Trials Group Protocol 190 Team. J Infect Dis 1997; 175 (5): 1039-50
57. Pizzo PA, Butler K, Balis F, et al. Dideoxycytidine alone and in an alternating schedule with zidovudine in children with symptomatic human immunodeficiency virus infection. J Pediatr 1990; 117: 799-808
58. Spector SA, Blanchard S, Wara DW, et al. Comparative trial of two dosages of zalcitabine in zidovudine-experienced children with advanced human immunodeficiency virus disease. Pediatric AIDS Clinical Trials Group. Pediatr Infect Dis J 1997; 16: 623-6
59. Delta Trial. Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. Delta Coordinating Committee. [published erratum appears in Lancet 1996 Sep 21; 348 (9030): 834]. Lancet 1996; 348 (9023): 283-91
60. Kline MW, Blanchard S, Fletcher CV, et al. A phase I study of abacavir (1592U89) alone and in combination with other antiretroviral agents in infants and children with human immunodeficiency virus infection. AIDS Clinical Trials Group 330 Team [letter; comment]. Pediatrics 1999; 103 (4): e47
61. Hervey PS, Perry CM. Abacavir: a review of its clinical potential in patients with HIV infection [in process citation]. Drugs 2000 Aug; 60 (2): 447-79
62. Hughes W, McDowell JA, Shenep J, et al. Safety and single-dose pharmacokinetics of abacavir (1592U89) in human immunodeficiency virus type 1-infected children. Antimicrob Agents Chemother 1999; 43: 609-15
63. Wang LH, Chittick GE, McDowell JA. Single-dose pharmacokinetics and safety of abacavir (1592U89), zidovudine, and lamivudine administered alone and in combination in adults with human immunodeficiency virus infection. Antimicrob Agents Chemother 1999; 43 (7): 1708-15
64. Saez-Llorens X, Nelson RP, Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. The CNAA3006 Study Team. Pediatrics 2001 Jan; 107 (1): E4
65. Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. Lancet 2002; 359 (9308): 733-40
66. Hetherington S, McGuirk S, Powell G, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. Clin Ther 2001; 23 (10): 1603-14
67. 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 (2): 368-74
68. Temesgen Z, Wright AJ. Antiretrovirals. Mayo Clin Proc 1999; 74: 1284-301
69. Luzuriaga K, Bryson Y, McSherry G, et al. Pharmacokinetics, safety, and activity of nevirapine in human immunodeficiency virus type 1-infected children. J Infect Dis 1996; 174: 713-21
70. Musoke P, Guay LA, Bagenda D, et al. A phase I/II study of the safety and pharmacokinetics of nevirapine in HIV-1-infected pregnant Ugandan women and their neonates (HIVNET 006). AIDS 1999; 13 (4): 479-86
71. Pollard RB, Robinson P, Dransfield K. Safety profile of nevirapine, a nonnucleoside reverse transcriptase inhibitor for the treatment of human immunodeficiency virus infection [review]. Clin Ther 1998; 20 (6): 1071-92
72. Bardsley-Elliot A, Perry CM. Nevirapine: a review of its use in the prevention and treatment of paediatric HIV infection. Paediatr Drugs 2000 Sep-Oct; 2 (5): 373-407
73. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. N Engl J Med 1999; 341 (25): 1874-81
74. Thuret I, Michel G, Chambost H, et al. Combination antiretroviral therapy including ritonavir in children infected with human immunodeficiency. AIDS 1999; 13 (1): 81-7
75. Melvin AJ, Mohan KM, Arcuino LA, et al. Clinical, virologic and immunologic responses of children with advanced human immunodeficiency virus type 1 disease treated with protease inhibitors. Pediatr Infect Dis J 1997; 16: 968-74
76. Mueller BU, Nelson Jr RP, Sleasman J, et al. A phase I/II study of the protease inhibitor ritonavir in children with human immunodeficiency virus infection. Pediatrics 1998; 101 (3 Pt 1): 335-43
77. Dumon C, Solas C, Thuret I, et al. Relationship between efficacy, tolerance, and plasma drug concentration of ritonavir in children with advanced HIV infection [in process citation]. Ther Drug Monit 2000 Aug; 22 (4): 402-8
78. Hsu A, Granneman GR, Cao G, et al. Pharmacokinetic interaction between ritonavir and indinavir in healthy volunteers. Antimicrob Agents Chemother 1998; 42 (11): 2784-91
79. Rutstein RM, Feingold A, Meislich D, et al. Protease inhibitor therapy in children with perinatally acquired HIV infection. AIDS 1997; 11: F107-11
80. Periard D, Telenti A, Sudre P, et al. Atherogenic dyslipidemia in HIV-infected individuals treated with protease inhibitors. The Swiss HIV Cohort Study. Circulation 1999; 100 (7): 700-5
81. Hagerty SL, Ascher DP. Spontaneous bleeding associated with the use of the protease inhibitor ritonavir in a hemophiliac patient with human immunodeficiency virus infection. Pediatr Infect Dis J 1998; 17 (10): 929-30
82. Mueller BU, Sleasman J, Nelson Jr RP, et al. A phase I/II study of the protease inhibitor indinavir in children with HIV infection. Pediatrics 1998; 102 (1 Pt 1): 101-9
83. van Rossum AM, Niesters HG, Geelen SP, et al. Clinical and virologic response to combination treatment with indinavir, zidovudine, and lamivudine in children with human immunodeficiency virus-1 infection: a multicenter study in the Netherlands. On behalf of the Dutch Study Group for Children with HIV-1 infections. J Pediatr 2000 Jun; 136 (6): 780-8
84. Gatti G, Vigano' A, Sala N, et al. Indinavir pharmacokinetics and parmacodynamics in children with human immunodeficiency virus infection. Antimicrob Agents Chemother 2000; 44 (3): 752-5
85. Fletcher CV, Brundage RC, Remmel RP, et al. Pharmacologic characteristics of indinavir, didanosine, and stavudine in human immunodeficiency virus-infected children receiving combination therapy. Antimicrob Agents Chemother 2000; 44 (4): 1029-34

86. Ascher DP, Lucy MD. Indinavir sulfate renal toxicity in a pediatric hemophiliac with HIV infection. Ann Pharmacother 1997; 31 (10): 1146-9
87. Gajewski LK, Grimone AJ, Melbourne KM, et al. Characterization of rash with indinavir in a national patient cohort. Ann Pharmacother 1999; 33 (1): 17-21
88. Babl FE, Regan AM, Pelton SI. Abnormal body-fat distribution in HIV-1-infected children on antiretrovirals [letter]. Lancet 1999; 353 (9160): 1243-4
89. Pollmann H, Richter H, Jurgens H. Platelet dysfunction as the cause of spontaneous bleeding in two haemophilic patients taking HIV protease inhibitors [letter]. Thromb Haemost 1998; 79 (6): 1213-4
90. Racoosin JA, Kessler CM. Bleeding episodes in HIV-positive patients taking HIV protease inhibitors: a case series. Haemophilia 1999; 5: 266-9
91. Sass JO, Jakob-Solder B, Heitger A, et al. Paronychia with pyogenic granuloma in a child treated with indinavir: the retinoid-mediated side effect theory revisited. Dermatology 2000; 200 (1): 40-2
92. Jarvis B, Faulds D. Nelfinavir: a review of its therapeutic efficacy in HIV infection [review]. Drugs 1998; 56 (1): 147-67
93. Krogstad P, Wiznia A, Luzuriaga K, et al. Treatment of human immunodeficiency virus 1-infected infants and children with the protease inhibitor nelfinavir mesylate. Clin Infect Dis 1999; 28 (5): 1109-18
94. Moyle GJ, Youle M, Higgs C, et al. Safety, pharmacokinetics, and antiretroviral activity of the potent, specific human immunodeficiency virus protease inhibitor nelfinavir: results of a phase I/II trial and extended follow-up in patients infected with human immunodeficiency virus. J Clin Pharmacol 1998; 38 (8): 736-43
95. Funk MB, Linde R, Wintergerst U, et al. Preliminary experiences with triple therapy including nelfinavir and two reverse transcriptase inhibitors in previously untreated HIV-infected children. AIDS 1999; 13 (13): 1653-8
96. Fortuny C, Vicente MA, Medina MM, et al. Rash as side-effect of nelfinavir in children [letter]. AIDS 2000; 14 (3): 335-6
97. Arpadi SM, Cuff PA, Horlick M, et al. Visceral obesity, hypertriglyceridemia and hypercortisolism in a boy with perinatally acquired HIV infection receiving protease inhibitor-containing antiviral treatment [letter]. AIDS 1999; 13 (16): 2312-3
98. Hurst M, Faulds D. Lopinavir. Drugs 2000; 60 (6): 1371-9
99. Saez-Llorens X, Renz C, Deetz C, et al. Kaletra (lopinavir/ritonavir) in HIV-infected children at 48 weeks [abstract 680]. Abstracts from the 8th Conference on Retroviruses and Opportunistic Infections; 2001 Feb 4-8, Chicago (IL)

Correspondence and offprints: Professor *John B. Ziegler*, Department of Immunology and Infectious Diseases, Sydney Children's Hospital, Randwick, NSW, Australia.
E-mail: j.ziegler@unsw.edu.au