

PENTA guidelines for the use of antiretroviral therapy, 2004

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There have been few major advances in paediatric HIV management over the last 2 years. Decisions about starting antiretroviral therapy can now be based on a recent large meta-analysis of the predictive value of CD4 and HIV RNA viral load (VL) in nearly 4000 untreated children, which is discussed in these updated guidelines. Risk estimates for progression to AIDS and death using surrogate markers can now be broken down by age, allowing more accurate discussion with families. In addition, there is increasing recognition of the problems of long-term adherence, drug resistance and cumulative toxicity in adults and children. The controversy over whether to treat asymptomatic infants continues. For older children more data on the efficacy of ritonavir boosted protease inhibitor (PI) regimens suggests that these may be the PI option of first choice. There is still no adult or paediatric trial evidence on which to base decisions about whether to start with PI- or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens, but the PENPACT 1 trial, which is addressing this question, is ongoing. There are increasing moves to provide simpler antiretroviral therapy (ART) regimens, including once daily dosing, but these lag behind adult regimens because of the paucity of pharmacokinetic data. Resistance assays should now be performed in all HIV-infected infants exposed to ART in pregnancy. Therapeutic drug monitoring may be very important in children because of high between- and within-child variability in drug absorption and metabolism. A trial to evaluate this should start shortly in Europe (PENTA 14 trial). The value of resistance tests for choice of second-line and subsequent choices of ART regimens remain unproven (the PERA trial will report late in 2004), but resistance assays are increasingly being used. The issue of when to switch therapy also remains unanswered and is being addressed within the PENPACT 1 trial. Regular formal assessment of adherence is now the standard of care, and routine monitoring in the clinic for lipodystrophy syndrome (LDS) and other ART toxicities is increasingly important. These guidelines will be updated again in 2006.

1. Introduction

The care of children with HIV infection in Europe is complex. The Paediatric European Network for Treatment of AIDS (PENTA) 2004 guidelines provide a review of the evidence base for treatment. They clearly demonstrate the marked limitations of the evidence and the strong continuing need for clinical trials within the PENTA network, particularly to address strategies aimed at reducing life-time toxicity of antiretroviral therapy (ART), while maintaining or increasing long-term efficacy. Many clinical and treatment issues cannot be covered in the guidelines. PENTA therefore believes that paediatric HIV specialists need to be involved in the care of all HIV-infected children, either directly or as part of a clinical

network. More work needs to be done to define specialist centres. There is also a need to improve the training of paediatricians specializing in the care of children with HIV.

The successful identification of HIV among pregnant women and reduction of perinatal transmission has dramatically reduced the number of children born with HIV in Europe. Perinatal transmission, however, is still high in some countries in Eastern Europe, and older children migrating from high prevalence countries continue to present to paediatricians in Europe with advanced disease. For these reasons and because HIV-infected children are living much longer with antiretroviral therapy, the number of children under care has increased in many European countries. Overall, the cohort of children with HIV in Europe is increasing in age and starting to enter adolescence. Many clinics are now collaborating with adult services to assist transition from paediatric to adult care. These 2004 guidelines were developed using a full review of Medline and international HIV conferences.

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Table 1 Levels of evidence and recommendations

Study design	Evidence level	Recommendation grade
Good recent systematic review	Ia	A +
One or more very rigorous studies	Ib	A –
One or more prospective studies	II	B +
One or more retrospective studies	III	B –
Formal combination of expert opinion	IVa	C
Informal expert opinion	IVb	D

Standard levels of evidence and grades of recommendations are used (Table 1). The guidelines have been approved by the PENTA Steering Committee.

The PENTA guidelines should be read in conjunction with both the US paediatric HIV guidelines (www.aidsinfo.nih.gov/guidelines) and national guidelines. The PENTA and US guidelines are now very similar with regard to when to start therapy, what to start with and the appropriate dosing of drugs.

The principles of care for children with HIV were laid out in the PENTA 2002 guidelines (www.pentatrials.org). The main changes since 2002 are an increased recognition of the toxicity associated with ART use, a greater emphasis on adherence monitoring and an increased awareness of the problem of drug resistance. Most children in Europe on ART are now well and are at school, however as they live longer on ART, greater numbers of children are developing resistant virus and ART toxicity. The aim now is to maximize the efficiency of highly active antiretroviral therapy (HAART) use, while minimizing long-term toxicity.

2. When to start treatment

2.1 Background

The PENTA 1 trial of early vs. deferred zidovudine monotherapy [1] remains the only randomized trial evaluating when to start ART in children. Recommendations on when to start combination therapy in both adults and children are based on cohort data that provide an estimate of the risk of progression to AIDS or death based on the child's current CD4 percentage and viral load (VL). Recommendations based on surrogate marker data cannot give an absolute risk. Emphasis should be placed on serial measurements of CD4%, VL and clinical assessment. VL and CD4% fluctuate with intercurrent illness, physiological and test variability. The trend in 3–4 repeated measurements of CD4% and VL is very important. Rapid clinical, virological or immunological failure is of particular concern. Starting ART is rarely an emergency. Time spent preparing and educating the family is never wasted.

Starting ART should be a fully informed choice supported by the family if it is to succeed. It is preferable not to start ART the first time you meet a family. Older children should know why they are taking treatment, with full or partial disclosure. With increasing recognition of the long-term problems of resistance and toxicity associated with ART, it should only be started when the risk of progression is 'significant', although consensus about the definition of 'significant' remains unclear. Risk assumptions should be discussed fully. Some families may be more risk averse, while in others concerns around the burden and toxicity of ART means they will accept a higher risk of clinical progression. There is a balance between the need for acting as the child's advocate with formal child protection in families rigidly opposed to ART, and respecting a family's need for time to adjust to the diagnosis and treatment.

Previous individual cohort data [2,3] including relatively small numbers of children gave risk analysis over a 2–7-year time period. CD4% and VL are now usually measured every 3–4 months in children under follow up in Europe, therefore short-term risk estimates are probably more useful. Detailed data on risk of clinical progression based on surrogate markers are now available from a large meta-analysis of pooled longitudinal data from 3941 children from eight cohort studies and nine randomized trials in Europe and USA [4]. In this analysis, both CD4% and VL were independent predictors of clinical progression, although CD4% was the stronger predictor. Risk levels also vary less with VL than CD4%, so less emphasis overall is placed in these guidelines on VL. Although CD4% is used in preference to absolute CD4 counts, which vary more with age in children, total and CD4 lymphopenia are strong predictors of clinical progression and should be used more in older children.

The meta-analysis now provides very useful risk levels for progression to AIDS or death over the subsequent 6 and 12 months using the child's current age, CD4% and VL [4]. Individual risk levels can be obtained from a calculator on the PENTA website (www.pentatrials.org). Table 2 provides a summary of the risk of progression to AIDS and death over the subsequent 12 months by current age and CD4%. Figures 1 and 2 show the same data graphically. Care must be taken in the interpretation of the risk generated from the meta-analysis for an individual child. The data is a pooled retrospective analysis of longitudinal cohorts and trials in the pre-HAART era, and a strong calendar time effect was observed. Although the analysis is adjusted for cotrimoxazole prophylaxis, it is very likely that progression to AIDS will be slower in prospectively followed children in 2004 than it was 10–15 years earlier. There could also be different practices and populations in individual countries that

Table 2 Risk of progression to AIDS and death over the next 12 months based on current age and CD4%

Age	CD4 5%		CD4 10%		CD4 15%		CD4 20%		CD4 25%		CD4 30%		CD4 35%	
	AIDS	Death	AIDS	Death	AIDS	Death	AIDS	Death	AIDS	Death	AIDS	Death	AIDS	Death
3/12	71	56	60	39	49	27	40	19	34	14	28	10	25	8
6/12	65	47	51	30	40	19	31	12	25	9	20	6	18	5
1	56	36	40	20	29	12	21	7	16	4	13	3	11	3
2	46	26	29	12	18	6	12	3	9	2	7	1	6	1
3	39	20	22	8	13	4	8	2	6	1	5	<1	5	<1
4	34	16	18	6	10	3	6	1	4	<1	4	<1	4	<1
5	31	14	15	5	8	2	5	<1	4	<1	3	<1	3	<1
6	28	12	12	4	6	1	4	<1	3	<1	3	<1	3	<1
7	26	11	11	3	5	1	3	<1	3	<1	2	<1	2	<1
8	24	10	9	3	4	<1	3	<1	2	<1	2	<1	2	<1
9	22	9	8	2	4	<1	2	<1	2	<1	2	<1	2	<1
10	20	8	7	2	3	<1	2	<1	2	<1	2	<1	2	<1

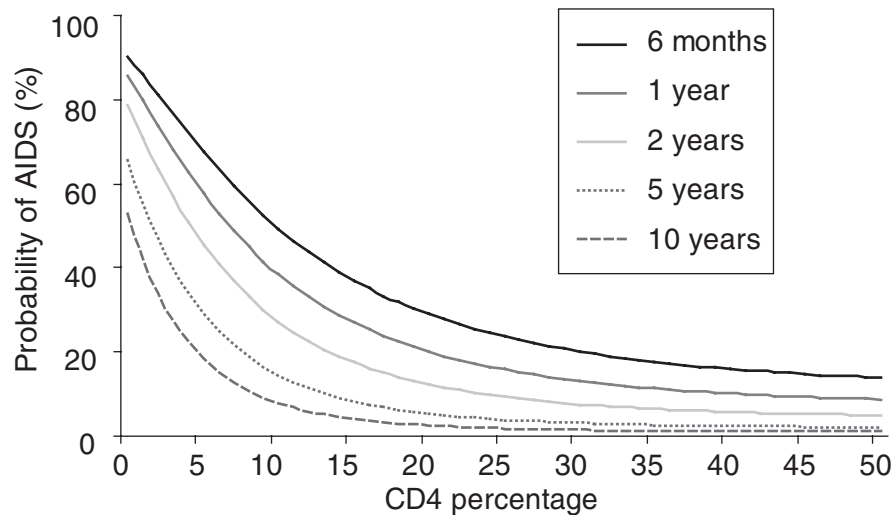


Fig. 1. Graph of probability of a child developing AIDS within the next 12 months by age and current CD4 percentage – from Dunn (2003) [4].

influence outcome. It is clear that surrogate marker-based risk of progression varies considerably by age, so in these PENTA guidelines we have used five age bands (< 1, 1–3, 4–8, 9–12 and 13–17 years). The risk of progression for each age band based on clinical, immunological and virological data from the meta-analysis [4] are discussed below.

In formulating these guidelines a risk of progression to AIDS in the subsequent 12 months of > 10% and a risk of death in the next 12 months of > 5% was considered to be unacceptable (based on data from the HIV Pediatric Prognostic Markers Collaborative Study (HPPMCS) analysis [4]). These are pragmatic levels and may change with time as further evidence of the efficacy and toxicity of ART become available. Combination ART is very effective in reducing the incidence of major new opportunistic infections and organ disease. There is a need to assess the more subtle risks of HIV progression in untreated children,

including mild cognitive impairment and organ disease, and balance these against the emerging long-term toxicity of HAART.

2.2 Infants

With the widespread uptake of antenatal HIV testing and perinatal interventions to reduce vertical transmission, few HIV-infected infants are born to HIV-infected women in Western Europe unless the mother's HIV diagnosis is unknown in pregnancy, or interventions have not been taken up or have failed due to advanced maternal disease.

Clinical data

Infants who present with clinical AIDS have a high risk of dying before receiving ART [5], therefore all infants presenting with clinical stage C disease should start ART

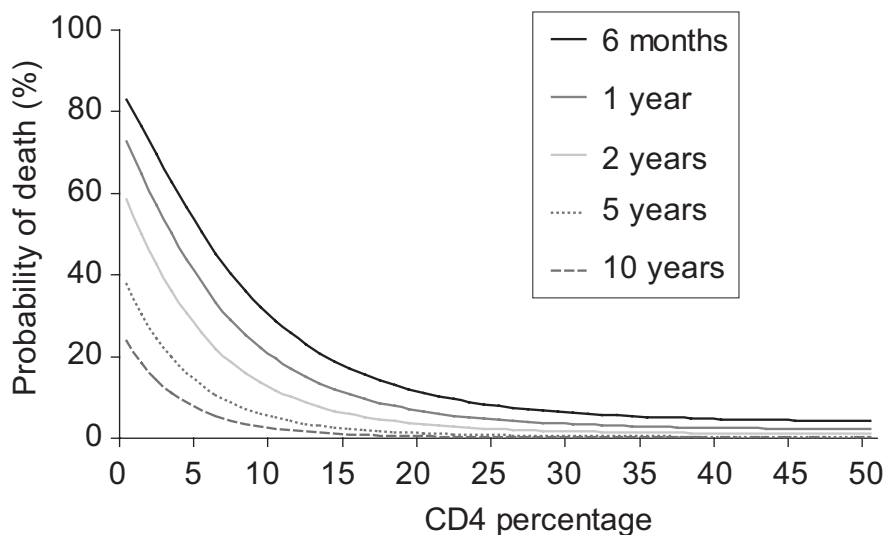


Fig. 2. Graph of probability of a child dying within the next 12 months by age and current CD4 percentage – from Dunn (2003) [4].

as soon as possible after treatment of their AIDS-defining illness. As discussed below, surrogate markers are poor predictors of rapid disease progression in infancy and rapid clinical deterioration often occurs in the presence of high CD4%. Infants not started on ART should therefore be very closely monitored clinically and for CD4 and VL values (e.g. every 1–2 months). Lymphadenopathy and/or hepatosplenomegaly (stage A disease) are not good indicators of clinical deterioration; failure to thrive or any stage B disease is an indication to start ART, as is any indication of neurodevelopmental deterioration.

Immunological and virological data

There is a complex balance between the immediate clinical and immunological benefits of early ART in asymptomatic infants, vs. concerns about the long-term development of resistance and toxicity to ART if initiated early. The major clinical concern is the development of an irreversible AIDS-defining illness, especially encephalopathy, because there are no good markers to determine which infants will develop rapidly progressive disease and which will be asymptomatic throughout childhood without treatment. Recent European cohort data in the era of widespread antenatal testing suggest that the development of encephalopathy is rare in prospectively identified and treated infants under care compared with historical controls [6,7]. Although it is theoretically possible that early therapy during primary infection can change the long-term outcome of the disease, this remains unproven in both adults and children.

There are also concerns about the early use of ART in asymptomatic infants. Infants often have very high VL values, and high rates of virological non-response [7] can

lead to the early development of resistance, limiting future treatment options [8,9]. Causes of poor response include inadequate pharmacokinetic levels, particularly for PIs [9], and poor adherence due to the difficulties of administering complex and unpalatable regimens to asymptomatic infants. Some infants started early on HAART lose HIV antibody and HIV-specific immune responses, probably related to the absence of HIV antigen presentation [10]. It may be possible to stop therapy in early childhood in some children treated in infancy, the hypothesis being that early limited ART has a long-term beneficial effect on the natural history of the disease. Trials addressing this question are being planned.

The high risk of short-term progression in infants means that it may be more appropriate to consider the risk of progression to AIDS or death over the next 6 months rather than 1 year. The meta-analysis data predict that at 6 months of age there is an approximate risk of developing AIDS in the subsequent 6 months of 10% when an infant's CD4% falls below 35%, increasing to a 15% risk of developing AIDS when the CD4% reaches 25%. At a chronological age of 6 months the risk of death over the subsequent 6 months increases to >5% when the CD4% falls below 25%. Within the limitations of the data discussed, infants with a CD4% between 30 and 35% and falling should start ART. It is still acceptable, after full discussion with the parents and documentation of the risks involved, not to treat asymptomatic infants with no evidence of clinical progression, with HIV RNA VLs of less than 1 million copies/mL, and a stable CD4% of over 35%. Many expert clinicians feel that the risk of progression is so high in infants that they would prefer to offer parents the option of treating all asymptomatic children identified in the first year of life. There are limited data

on other clinical indicators that may suggest an increased likelihood of more rapid disease progression in the infant. These include advanced maternal disease, and other viral co-infection, for example cytomegalovirus (CMV) infection.

2.3 Children

Clinical data

All children with an AIDS defining illness should start ART following discussion with their family. The evidence for clinical benefit of ART in children with AIDS is so strong that complete parental refusal to treat is now a child protection issue in Europe. Symptomatic disease (stage B) includes conditions with differing predictive values. In particular, children with lymphocytic interstitial pneumonitis (LIP) may have a stable clinical course many years after diagnosis apart from recurrent chest infections [11].

Immunological data

Adult cohort data suggest no additional benefit of starting ART with a CD4 count of > 350 cells/mm³ compared with a CD4 count of 200–350 [12]. An adult CD4 count of 200 is the equivalent of approximately 13%. The trend in the rate of decline of CD4 count and percentage on repeated measurements is also important. A CD4 decline of over 100 cells or $> 2\%$ per month is a poor prognostic sign in adults [13]. In children the prognostic significance of a specific CD4 percentage changes with age, as discussed below.

1–3 years old. The risk of encephalopathy and rapid clinical progression is still high in this age group. It is therefore more appropriate to use a CD4 percentage of < 20 as the trigger to initiate therapy.

4–8 years old. Previous PENTA guidelines used a cut off CD4 count of $< 15\%$ for the initiation of therapy. This corresponds to an adult absolute count of around 250 cells/mm³. Within this age band, data from the meta-analysis suggest that a CD4% of 15% is still an appropriate level to start therapy. Discussion with the family, however, should be initiated at higher levels and a CD4% of 15% considered at the lower end of the range for treatment initiation; it would not be considered safe to delay therapy in a child with a rapidly falling CD4% below 15%.

9–12 years old. From the meta-analysis data, death was very rare in older children with a CD4% $> 10\%$, the 1-year risk of progression to AIDS being well under 10%. Although a CD4% of 15% is still a reasonable level to initiate therapy in this age group, there is less urgency than in the younger child. Absolute CD4 count can also be used to guide ART in this age group (CD4 200–350 cells/mm³, consider ART; CD4 < 200 cells/mm³, must start ART).

13–17 years old. There are few data on the risk of progression in newly diagnosed adolescents. In parts of

Europe, increasing numbers of older children are presenting who were born and spent their early childhood in high prevalence countries (some are long-term non-progressor). There is a need for further data in this group. At present it seems reasonable to use current adult guidelines for starting therapy within the range of CD4 absolute count between 200 and 350 cells/mm³. Social and adherence factors are often critical to the success of ART in adolescents.

HIV RNA viral load

VL is an independent predictor of progression to AIDS and death, although its prognostic significance is weaker than CD4%. Children with low VLs (< 4 log) are unlikely to progress rapidly. There is variation between different laboratory methods (especially at the extremes of measurement), and all results should be repeated. Data from the meta-analysis show that the VL threshold for a risk $> 10\%$ of a child developing AIDS during the subsequent year varies according to age.

- For infants a VL $> 1000\ 000$ copies/mL is associated with a risk of developing AIDS over the subsequent year of $> 10\%$.
- For children aged 1–3 years a VL $> 250\ 000$ copies/mL is associated with a risk of developing AIDS over the subsequent year of $> 10\%$.
- For children aged 4–12 years, an approximate VL of $> 250\ 000$ copies/mL is associated with a risk of developing AIDS over the subsequent year of $> 10\%$.
- Children with a VL of $< 10\ 000$ copies/mL at all ages up to 12 years have a risk of developing AIDS over the subsequent year of $< 3\%$.

A summary of when to start ART is given in Table 3.

3. Which ART regimen to start

There are no adequately powered randomized trials allowing direct comparison of different HAART regimens in children. The PENPACT1 trial is a collaboration between PENTA and the Pediatric AIDS Clinical Trials Group (PACTG) in which children are randomly assigned to start ART with either a protease inhibitor (PI)- or a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple ART regimen. Paediatricians are strongly encouraged to enter children into this trial, pending further data from adult trials, which may anyway be difficult to interpret because CD4 and VL as surrogate markers behave differently in children compared with adults. Care should be taken with interpretation of the many small non-randomized paediatric cohort studies discussed below. Discussion with the family about which antiretroviral drugs to start should include consideration of the taste and

Table 3 Summary of recommendations on when to start antiretroviral therapy – grade A +

<p>Infants</p> <p>1. Clinical</p> <p>Start all infants with CDC stage B or C (AIDS) disease.</p> <p>2. Surrogate marker</p> <p>Start all infants with CD4% <25–35%.</p> <p>Strongly consider starting with a VL >1 million copies/mL.</p> <p>Many experts treat all asymptomatic infants.</p> <p>Children aged 1–3 years</p> <p>1. Clinical</p> <p>Start all children with stage C disease.</p> <p>2. Surrogate marker</p> <p>Start all children with a CD4% <20%.</p> <p>Strongly consider starting with a VL >250 000 copies/mL.</p> <p>Children aged 4–8 years</p> <p>1. Clinical</p> <p>Start all children with stage C disease.</p> <p>2. Surrogate marker data</p> <p>Start all children with a CD4% <15%.</p> <p>Strongly consider starting with a VL >250 000 copies/mL.</p> <p>Children aged 9–12 years</p> <p>1. Clinical</p> <p>Start all children with stage C disease.</p> <p>2. Surrogate marker data</p> <p>Start all children with CD4 <15%, but with less urgency than in a younger child.</p> <p>Strongly consider starting with a VL >250 000 copies/mL.</p> <p>Adolescents aged 13–17 years</p> <p>1. Clinical</p> <p>Start all adolescents with stage C disease.</p> <p>2. Surrogate marker data</p> <p>Start all adolescents with a CD4 absolute count between 200 and 350 cells/mm³.</p>
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volume of syrups, pill size and numbers, crushability, storage and food requirements, and number of times a day drugs must be taken. It is good practice to show the family the medicines at an early stage. Details of early (e.g. nausea, vomiting, diarrhoea) and late side-effects of drugs should be discussed and documented. A meta-analysis of studies in adults recently demonstrated the prognostic importance of the initial tolerability of the medicines in HIV patients who have started potent antiretroviral therapy [14].

3.1 Infants

Treatment in infants is difficult, because drug absorption, interactions and metabolism differ from older children, and higher doses may be required to achieve adequate drug levels. In addition, many infants have very high VL values. The results of early treatment including a PI in 31 infants in the French perinatal cohort showed a high frequency of virological failure, and VL levels less than 500 copies/mL were observed in only 53% of children after 6 months and 18% after 24 months on therapy. Failure was associated with genotypic resistance relatively early (e.g. at 6 months),

Table 4 Summary of recommendations on which ART to start – grade B +

<p>Infants</p> <p><i>either</i></p> <p>2 NRTI¹ + 1 PI (Lopinavir/r or Nelfinavir)</p> <p><i>or</i></p> <p>2 NRTI¹ + 1 NNRTI (Nevirapine)</p> <p>Children</p> <p><i>either</i></p> <p>2 NRTI¹ + 1 PI (Lopinavir/r or Nelfinavir)</p> <p><i>or</i></p> <p>2 NRTI¹ + 1 NNRTI (Efavirenz or Nevirapine²)</p>

¹Dual NRTI combination recommended: zidovudine plus lamivudine or didanosine; didanosine plus lamivudine; abacavir and lamivudine. D4T is not recommended as first-line therapy.

²Nevirapine would be the preferred NNRTI for children under age 3 years of age.

even with protease inhibitor drugs, demonstrating that resistance may develop rapidly when drugs are given with on-going high viral turnover [8]. Sub-optimal doses of drugs or incomplete adherence could contribute to treatment failure. Nevertheless, among the infants treated with ART before the age of 6 months only one child developed an opportunistic infection during the first 18 months of life and none developed encephalopathy. This represents a significant decrease in HIV disease progression compared with natural history data in the pre-HAART era [6].

Data on nelfinavir (NFV) in combination with stavudine (d4T) and didanosine (ddI) were reported in 20 infants enrolled in the PENTA 7 Study. Only 39% had a VL <400 copies/mL and 22% <50 copies/mL by week 48, although most infants were receiving the higher NFV dose of 150 mg/kg/day [9]. It has now been demonstrated that this or even higher doses of NFV are required for infants younger than 1 year to achieve NFV concentrations close to the minimum therapeutic levels reported in older children and in adults [15]. A protease-sparing regimen with four drugs (zidovudine [ZDV] + lamivudine [3TC] + abacavir [ABC] + nevirapine [NVP]) is reported to be effective by Tudor-William and co-workers [16]. Fifteen out of 17 infants achieved undetectable VLs (<400 copies/mL) by a median of 16 weeks and all were consistently undetectable at week 48, with subsequent normalization of CD4 counts and weight for age. NVP is at the moment the only NNRTI syrup available for infants, because the correct dose of efavirenz (EFV) for children aged under 3 years has not yet been identified.

3.2 Children

3.2.1 PI-based combinations

The first two studies of PI-based triple regimens (two nucleoside reverse transcriptase inhibitors (NRTIs) plus ritonavir (RTV) (PACTG 338 trial) and NRTIs plus NFV

Table 5 Advantages and disadvantages of specific ART drugs

Combinations with best clinical evidence	Pro	Contra
NRTI		
AZT + 3TC	<ul style="list-style-type: none"> - best results in adult ACTG 384 - palatable liquid formulation - co-formulation in a single pill 	<ul style="list-style-type: none"> - bone marrow toxicity
AZT + ddl	<ul style="list-style-type: none"> - extensive experience - ddl in a single pill for a o.d. dose 	<ul style="list-style-type: none"> - bone marrow toxicity - pancreatic toxicity - food interference
3TC + ABC	<ul style="list-style-type: none"> - no food interference - palatable liquid formulation - can be given once daily 	<ul style="list-style-type: none"> - potential ABC hypersensitivity
D4T + 3TC	<ul style="list-style-type: none"> - palatable liquid formulation - no food interference - synergetic activity 	<ul style="list-style-type: none"> - d4T toxicity: lactic acidosis, lipotrophy, peripheral neuropathy
zdv + ABC	<ul style="list-style-type: none"> - palatable liquid formulation - no food interference 	<ul style="list-style-type: none"> - potential ABC hypersensitivity - bone marrow toxicity
ddl + 3TC	<ul style="list-style-type: none"> - possibility of once daily administration 	<ul style="list-style-type: none"> - food interference - pancreatic toxicity
Not recommended		
zdv + d4T		<ul style="list-style-type: none"> - drug interaction
ddl + d4T		<ul style="list-style-type: none"> - higher combined risk of lipodystrophy
NNRTI		
NVP	<ul style="list-style-type: none"> - liquid formulation - no food interactions 	<ul style="list-style-type: none"> - resistance with single mutation - rash and hepatic side-effects
EFV	<ul style="list-style-type: none"> - once day administration - no food interaction 	<ul style="list-style-type: none"> - resistance with single mutation - neuro-psychiatric side-effects
PI		
LPV/r	<ul style="list-style-type: none"> - high syrup concentration, low volumes - high genetic barrier 	<ul style="list-style-type: none"> - poor taste of syrup - large capsules
NFV	<ul style="list-style-type: none"> - few adverse effects - should be given with food 	<ul style="list-style-type: none"> - diarrhoea - high variability in blood levels - high pill burden
RTV		<ul style="list-style-type: none"> - poor palatability - gastrointestinal intolerance

Table 6 New ART either currently or soon available

Drug	Class	Advantages	Problems	Tolerance in children
Tenofovir	Nucleotide reverse transcriptase inhibitor (NA)	Once daily; Low mitochondrial toxicity profile	Some cross resistance with NA	Nephrotoxicity – tubular leak osteoporosis
Emtricitabine	Nucleoside reverse transcriptase inhibitor	Once daily	Cross resistance to 3TC	Unknown
Atazanavir	Protease inhibitor	Once daily; Low incidence of lipid disturbance	Cross resistance to other PIs Ritonavir boosting required	Hyperbilirubinaemia
Tipranavir	Protease inhibitor	Active in PI-resistant virus	Must be boosted by ritonavir	Unknown
Fosamprenavir	Protease inhibitor	Pro drug of amprenavir Lower pill burden	Must be boosted by ritonavir	Unknown
Enfuvirtide (T20)	Fusion inhibitor	New class; No cross resistance	Subcutaneous injection twice/day	Painful local reaction

3TC, lamivudine.

(PACTG 377) reported that approximately 40–50% of children receiving these drugs achieved plasma HIV-1 RNA of <400 copies/mL by 24 weeks. Poor results in PACTG 338 could be due to the unpleasant taste and poor gastrointestinal tolerability of RTV. In PACTG 377 a higher proportion of children receiving a four-drug regimen including all three classes of drugs appeared to respond virologically compared with those on three-drug regimens,

but numbers were small [17,18]. In adults, there are no convincing data suggesting that four-drug regimens are more effective than three-drug regimens, and because data are sparse in children this should not normally be recommended.

In the PENTA 5 trial, dual NRTI combinations of ZDV, 3TC and ABC were compared with or without NFV in 128 previously untreated children. Sixty-four per cent of all

children achieved an HIV RNA VL of <400 copies/mL (despite about 20% of them being only on two drugs). At week 48, significantly higher VL responses were observed in the ABC-containing arms (>70% with VL of <400 copies/mL; around 50% at <50 copies/mL) compared with ZDV and 3TC (44% and 31% at <400 and 50 copies/mL, respectively) and this difference continued out to 3 years follow-up when approximately 60% of children were still on therapy as randomly assigned. Where viral rebound did occur, however, it was more likely to be associated with resistance in the 3TC + ABC arm than in the ABC + ZDV arm, which may be of concern if this combination is used in combination with NVP or EFV, which have low genetic barriers to resistance, particularly in very young children with high VL or if non-adherence may be an issue. Further work to evaluate resistance patterns after 3 years is on-going in the PENTA 5 trial.

PENTA 5 is the only paediatric trial to compare NFV with placebo, but was powered only to compare toxicity between the two arms. Diarrhoea was more common in the NFV group but was mild and did not result in drug discontinuation. Clinical evidence of lipodystrophy was reported in only 2% of children after 2 years of follow-up [19]. NFV powder was very poorly tolerated and nearly all children switched to crushed tablets, although the pill burden was high for older children [20]. Preliminary results on the new formulation of NFV (625 mg tablets) have reported a marked reduction in the incidence of serious diarrhoea in adults (from 11.1% to 6.5%) and better bioavailability [21], but these tablets are more difficult to crush.

The large non-randomized study of Saez-Llorens *et al.* [22] demonstrated that the liquid formulation of lopinavir and ritonavir (LPV/r) is safe and well tolerated by HIV-infected children. The high syrup concentration means low volumes are needed, although the taste of the liquid is still poor and the capsules are large. Substantial and persistent antiviral activity and improved immune function were observed in 88% of the ART-naïve/PI-naïve enrolled subjects, with 69% of children achieving a VL of <50 copies/mL at week 48. Despite the concern over possible increased long-term lipodystrophy with a ritonavir-boosted PI, the improved VL and CD4 data suggest that first-line PI use in children should possibly be ritonavir-boosted, as in adults. Paediatric data from the other new ritonavir boosted PIs, fos-amprenavir, atazanavir and tipranavir are awaited.

3.2.2 NNRTI-based combinations

Due to the major concerns about metabolic toxicity associated with PI use, there is increasing interest in NNRTI-based combinations as first-line regimens. Data from adult studies

have reported good VL responses with NNRTI-based first-line regimens even in patients with high VLs [23,24]. The analysis of the ACTG 384 trial data suggested that the efficacy of EFV was superior to that of NFV when combined with AZT/3TC as first-line ART [25]; however, there remain few data on NNRTI use in children. A UK retrospective analysis of 74 children on NVP-containing regimens in previously untreated (38%) and ART-experienced children reported good clinical and immunological responses, but with the best virological response being observed in children receiving doses of NVP greater than 300 mg/m²/day [26]. Dosing of NVP using a surface area formula is preferable than using the mg/kg recommendations, because the latter was not used in clinical trials, generally results in lower doses and recommendations include a curious step in recommended dose at age 8 years that is not evidence-based. The PACTG study 382 combining efavirenz with nelfinavir reported 76% of children with a VL of <400 and 63% <50 copies/mL at week 48, however these children had low VLs (approximately 10 000 copies/mL) at baseline [24]. Other observational studies have reported good surrogate marker data with EFV-based regimens; CNS side-effects being the main toxicity [27].

3.2.3 Triple NRTI-based regimens

There remains concern about a worse outcome in adults treated with triple NRTI combinations, including ABC compared with NNRTI- or PI-based regimens, particularly if they have a very high VL or CDC stage C disease (AIDS). Although 48 week results from CNA 3014 show a similar response to abacavir and indinavir for adults with VLs of >5 log copies/mL at baseline [28], adult treatment guidelines no longer recommend triple NRTIs for first-line therapy. On-going studies in adults are evaluating a strategy in which patients initiate therapy with ABC/AZT/3TC plus a fourth agent and then discontinue the fourth agent after a period of time (>6 months) and after the individual has a VL of <50 copies/mL (simplification) [29]. Triple NRTI regimens may also be of value if children are on antituberculosis treatment too. Switching to the simple regimen of trizivir (AZT + 3TC + ABC) as one pill twice daily may be considered in older children and adolescents if pill burden is determined to be a major determinant of adherence (see simplification below) [30].

3.3 Once daily therapy

Although not proven, it is likely that adherence will be improved using once daily regimens. Recent data from PENTA 13 suggests that both 3TC and ABC pharmacokinetics supports once daily dosing in children as in adults [31]. Paediatric safety, effectiveness and dosing of new antiretrovirals, such as emtricitabine (FTC) [32] and

tenofovir (TDF) are now being established in children based on once daily dosing [33,34]. Recently, a once-a-day regimen based on emtricitabine (6 mg/kg) with ddi and EFV was evaluated in therapy-naïve children in the PACTG 1021 [35] and in the FTC-203 [36] studies. In the intent-to-treat analysis at week 16, 87% of children had a VL of <400 copies/mL and 74% <50 copies/mL [36]. It is likely that in the future children will be given once daily regimens wherever possible. It will be very important to ensure that pharmacokinetic data fully support once-daily regimens before they are used, particularly in younger children, in whom half-lives may be shorter.

3.4 Induction/maintenance and simplification

Recent results from the FORTE trial have supported the idea of an intensive induction phase of treatment, followed by a maintenance phase with a reduced number of antiretroviral drugs (four drugs, reducing to three drugs) [37]. Further trials to evaluate this approach in adults and children are needed. Simplification of therapy could include using a ritonavir boosted PI regimen initially, then switching to an NNRTI or triple NRTI regimen. A first PI to EFV switch study in 17 children showed continued undetectable VLs in 16/17 children at 48 weeks, stable CD4% values and a significant decrease in blood lipid levels after switching to EFV [38].

3.5 Planned (structured) treatment interruptions (PTIs)

With increasing concerns about long-term drug toxicity, trials evaluating the safety of intermittent ART are underway in adults. As CD4 count, and to a lesser extent CD4 percentage, decreases naturally with age in uninfected children, and the regenerative capacity of the thymus is high in HIV-infected children, the CD4 response to re-initiation of ART after interruption may be different (and better) in children compared with adults. Potential benefits of PTIs could include reduced toxicity and cost. Potential problems could be increased resistance leading to immunological failure and worsening adherence. A recent cohort study of 58 non-structured treatment interruptions in 51 children noted an average absolute fall in CD4% of 0.5% per month (similar to adults), with a wide range in the rate of fall, which appeared to be unrelated to pre-therapy or pre-interruption values [39]. The PENTA 11 trial is a randomized phase II trial to evaluate the safety of PTIs, where duration will be driven by the rate of CD4 decline. As in adults, treatment interruptions are currently not recommended outside a clinical trial setting.

3.6 Immune reconstitution syndrome

This syndrome has been increasingly recognized in adults starting ART with very low CD4 cell counts. Symptoms, which may be similar to those of an opportunistic infection, occur around 6 weeks later concurrent with a rapid rise in CD4 cell count. It has been reported infrequently in children, but may become more common in Europe as an increasing proportion of children under care present with late HIV disease having been born and acquired HIV elsewhere. It may be difficult to differentiate from recurrence of an opportunistic infection already present at the start of ART. Systemic steroids may be useful and ART should be continued.

Table 4 gives a summary of which ART to start with. Table 5 gives the advantages and disadvantages of specific combinations and Table 6 lists newer antiretroviral drugs.

4. Treatment failure

The failure of first-line therapy may be virological and/or immunological and/or clinical. Treatment failure is usually virological first, followed by immunological and eventually clinical failure. Clinical failure can be simply defined as the recurrence or non-disappearance of B and C disease. Similarly, immunological failure may be considered as the non-correction or reappearance of low CD4 percentage (generally 20%, but could be lower in older children, or CD4 count in adolescents). The definition of virological failure is more complex and a consensus has not yet been reached. The overall aim of treatment is to reduce VL to levels below the lowest detection threshold (<50 copies/mL) as rapidly as possible and to maintain undetectable levels for as long as possible. A large number of children on treatment, however, have a detectable VL between 1000 and 50 000 copies/mL, but continue to have excellent clinical response and maintain high CD4% values. The presence of continued viral replication is associated with increasing cumulative risk of the acquisition of resistance mutations, which may eventually drive immunological and clinical failure as well as compromise subsequent combinations, due to the cross-resistance induced by many resistance mutations. There have been few longitudinal studies of the emergence of resistance mutations in children, but there is no reason to believe that the data obtained in adults differ from those in children. There is, therefore, a general risk of resistance linked to the rate of residual viral replication, although this risk depends on the drugs used. The cut-off point defining 'acceptable' levels of residual VL and its duration have not yet been determined. The second randomization in the PENPACT 1 trial is evaluating the long-term virological efficacy of switching therapy at VLs of 1000 or 30 000

copies/mL. There are no on-going trials evaluating when to switch therapy in adults.

4.1 Causes of failure

Poor adherence, inadequate pharmacokinetic levels or inadequate potency of the drugs chosen can all contribute to antiretroviral treatment failure. Genetic differences in drug metabolism are also likely to be important. Drug level variability is high in children, who may benefit from individual 'tailoring' of drug doses following drug level measurement [40]. A trial addressing the value of single level and more complex area under curve (AUC) level therapeutic drug monitoring compared with no monitoring (PENTA 14 trial) is due to start shortly in Europe. Adherence support for all children will be included in this trial.

Assuming an appropriate choice of combination ART, administration of the correct doses, the absence of major pharmacokinetic interaction and normal digestive absorption, the leading cause of failure of the first-line treatment is poor or non-adherence. If poor adherence is identified and improved early, it may not necessarily lead to resistance. NNRTIs, however, are particularly likely to select mutations conferring complete resistance to the class within only a few days of viral replication.

4.2 Second-line treatment after initial treatment failure

The choice of treatment should be based on careful analysis of the causes of failure, the previous regimen used and possibly on the results of resistance genotyping. If, for example, a genotype shows no resistance mutations, non-adherence may be very likely and would suggest improving this rather than switching therapy. An alternative combination of drugs that are easier to take may be appropriate. If the child was initially treated with two NRTIs and one NNRTI, a general consensus is to use two new NRTIs and a PI. If, however, the child was treated with two NRTIs and a PI, the choice may include switching to two NRTIs and a NNRTI, but could also include a different ritonavir-boosted PI, if cross-resistance is not a risk.

4.3 Multiple ART failure

The problem of multidrug resistance is growing in paediatric HIV. Specialist advice is needed to interpret resistance test results showing complex combinations of mutations and to make recommendations about future treatment options. Below are some general principals about the treatment of children who have already received and failed two or more regimens. It is sometimes possible to reintroduce drugs previously prescribed to the child that

were originally poorly tolerated. This may be the case, for example, for drugs such as didanosine (now available in the form of enteric coated capsules). Reintroducing drugs for which resistance mutations have been identified in the past, but do not seem to be present in the most recent genotype evaluated is likely to result in rapid selection of the mutant strain, which although undetectable at the time of testing has been archived in long-lived cells. Below are some principles for salvage treatment.

- The use of new drugs, evaluated in adults, but for which paediatric use has not yet been fully evaluated may be justified (possibly with some measurement of drug levels if available). Ideally, this should be done within the framework of a formal protocol, but programmes with expanded access may be available. It is now possible to obtain several new drugs in this way. If these drugs are to be effective, they must be included with a regimen containing at least one other and ideally two new active agents to achieve the best chance of success. It is better to wait and change when three new drugs are available. It is very unwise unless really necessary to add a new drug to a failing regimen.
- Salvage combinations may include more than three drugs. Combinations of four or five drugs are possible (Mega-HAART). The combination of both NNRTIs currently available (NVP and EFV) in the same regimen has been shown to be of no value in a controlled study in adults. For NRTIs, only the combination D4T and ZDV clearly has an antagonistic effect on viral replication. Independent of the pharmacological boost given to certain protease inhibitors by ritonavir, combinations of two PIs are possible, but may result in complex pharmacological interactions with other drugs. Monitoring serum concentrations is strongly recommended. Mega-HAART regimens have a high risk of poor tolerability, cumulative toxicity and adherence problems.
- Even in the absence of a mutation conferring resistance specific to a new PI, the susceptibility of a resistant strain to other molecules of this class may be altered, with an increase in IC_{50} , necessitating the use of higher doses. There are adult data suggesting that the dose of lopinavir/r should be increased in patients with NNRTI or PI resistance.
- The potential value of a planned treatment interruption before the introduction of a new drug combination in order to allow wild-type, sensitive virus to flourish for a limited period, remains a matter of debate. No data are available for children. A recent randomized trial in adults [41] showed that, in highly pre-treated adults, morbidity is higher after treatment interruption for 4 months than after immediate introduction of a new regimen.

- In children that have persistent severe immune deficiency, but with virological control, interleukin 2 (IL2) may make it possible to increase CD4 counts significantly [42]. Unpublished data suggest that this effect may also occur even in the presence of very high levels of viral replication. A small trial comparing IL2 with no IL2 is due to start through PENTA and PACTG in Europe (PENPACT 2) and large clinical endpoint trials are ongoing in adults.

4.4 Resistance assays

Drug resistance may develop with only one mutation or may require several. Single mutants are often present within the virus quasi-species prior to treatment, and are selected by replication in the presence of the antiretroviral drug. For some drugs a single point mutation is associated with resistance (3TC or NNRTIs), while for other drugs (ABC, TDF or PIs) a number of mutations may be required for resistance to develop. Resistance can be overcome for certain drugs by increasing drug levels, for example PIs with RTV boosting. Resistance to antiretroviral drugs may be assessed by phenotypic or genotypic assays. Currently, only genotyping is routine. The PENTA 8 (PERA) trial is a randomized study of 171 children evaluating the role of resistance assays in children. Results of this study should be available during 2004.

At present a genotypic resistance assay should be performed in all HIV-infected infants exposed to any ART during pregnancy, and in children failing their second or subsequent regimens. If a resistance assay is not performed a sample should be stored for subsequent analysis if necessary. A list of the common resistance mutations is shown in Table 7.

4.5 Therapeutic drug monitoring (TDM)

The link between plasma concentrations of antiretroviral drugs and efficacy has been strongly suggested in several retrospective or observational studies, mainly for NNRTIs and PIs. The PENTA 14 study is a randomized trial comparing different levels of TDM in children compared to no TDM. Data on target normal ranges for drug levels in children are very limited. Approximate adult peak and trough ranges are given in Table 8. At present drug monitoring should be considered in children failing PI- or NNRTI-containing regimens, treatment with another antiretroviral or other drug having a potential interaction (e.g. PI/NNRTI combination), and in infants and children on drugs where dosage recommendations are based on very limited data. Further information is available at www.hiv-druginteractions.org.

Table 7 Common HIV mutations and associated ART resistance

Resistance mutations	ART associated resistance
NRTIs M41L, D67N, K70R, L210W, T215 Y, K219Q, K219E	TAMs (thymidine associate mutations) High level resistance to most NRTIs except 3TC
M184V 69 Insertions	3TC Occur after TAMs High level resistance to most NA
K65R Y115F L74V	ABC TDF ABC ddl
NNRTIs K103N Y181C Y188C	EFV and NVP NVP and EFV
PIs D30N N88D N88S L90M G84V V82A V82T V82F I47V I50V I84V L10I L10F K20R K20M M36I M46I M46L I54V I54L A71V A71T	NFV and other PIs SQV and other PIs RTV IDV and other PIs APV LPV and other PIs Increasing number of mutations seen on failing therapy High level resistance to most PIs

Table 8 Target ART trough and peak plasma concentrations (C_{min} , C_{max} , ng/mL) (data taken from studies on adults)

Nevirapine	3500–8000
Efavirenz	1000–5000
Indinavir	150–800
Nelfinavir	1000–4000
Saquinavir	100–3000
Amprenavir	400–3000
Lopinavir	1000–8000

5. Adherence

There is evidence that adherence to HAART predicts and is related to the virological and clinical response to therapy [43]. Therefore an important challenge when starting therapy is to convince parents and children to be fully adherent to the treatment regimen. Poor family social circumstances compound adherence difficulties, and careful social assessment and plans for family support should always precede starting or changing therapy. When changing therapy because of poor adherence, it is important to recognize that treatment failure is not always overcome by more simple regimens.

A high level of adherence to the complex antiretroviral regimens is critical for virological efficacy because resistance develops rapidly when drug levels are not maintained within a therapeutic range, rendering these drugs ineffective in the future as well as other antiretrovirals of the same class as a result of cross-resistance. Adult studies have found that more than 90% adherence with

antiretroviral medications is required for prolonged viral suppression [44,45]. A study in adults using pill bottles with computer chips to record dosing (medication event monitoring system, MEMS) found that the probability of treatment success was high (90%) if adherence was excellent (>95% of doses), but fell to 47% when adherence was 80–95% and dropped to only 13% if adherence was <80% [45]. It has also been demonstrated in children that greater than 80% adherence, assessed by MEMS, is associated with achieving a VL below 400 copies [46]. In children adherence may be suboptimal [46,47] because of complex factors relating to the child, the caregivers, the medication and their inter-relationships. Barriers to adherence in children include the lack of liquid formulations of some drugs, high volume, poor palatability, high pill burden, frequent daily dosing requirements, dietary restrictions and toxicity. In addition, specific psychological issues in children include the knowledge of their HIV status and the concern of the patient or caregiver about the disclosure to other family members, friends or school [48].

In the PACTG 377 trial there was a trend towards poorer adherence with regimens of four drugs, and with regimens including medications requiring three times daily dosing. Poor adherence to PI drugs was related to poor palatability leading to children refusing to take them [43]. In children some medicines can now safely be given once a day (3TC, ABC, ddI, FTC, EFV, TDF). In PENTA 5, one of the few prospective studies carried out on adherence, difficulties in taking the medications in the study were more frequently reported in the first months of therapy, suggesting that more efforts to improve adherence should be put in place at the initiation of therapy and when a new regimen is started [49].

5.1 Measuring adherence

There is no gold standard direct method for measuring adherence. A number of indirect methods and strategies have been used to assess adherence in clinical studies. Most studies in children have been cross-sectional and used single methods to measure adherence, such as self-report, caregivers interview or questionnaire [43,47,48]. The number of doses missed in the preceding week [43,49] has been shown to be a useful measure of adherence. Various aids for monitoring adherence have been proposed (www.bhiva.org/chiva and see www.fstrf.org/qol/ql_forms.html). Receipt of medication should be monitored using pharmacy records [43,46,48,50], and a paediatric pharmacist is an important member of the clinical team. Drug level monitoring may be useful, but can only be used as a guide because inter-individual variability is high in children, and finding a correct plasma level on the day of the sample does not guarantee that compliance is continuous.

Some form of formal evaluation of adherence should ideally be integrated into routine childcare. Regular (every 3–6 months) assessment of adherence performed by questionnaire can be useful. This should be combined with pharmacy record information and documented in the clinical notes. Despite the advances in simplifying anti-retroviral regimens and in monitoring adherence, many children are non-compliant and intervention is required. If possible, supervised administration with the help of family members, specialist nurses, psychologists and social organizations should be attempted. In selected cases, and particularly if drugs are poorly tolerated by mouth, a gastrostomy (G) tube may be a useful option to improve adherence. In some studies with small numbers of patients, G-tubes have been well tolerated by younger HIV-infected children, and caregivers have been satisfied with the procedure because it resulted in shorter medication administration times, fewer behavioural problems and better adherence and virological response [51,52]. They can be removed once the child is taking oral medication well.

6. Toxicity

Although there are fewer data on toxicity in children than in adults, the complete spectrum of metabolic complications observed in adults has been reported in children. The increasing prevalence of reported metabolic abnormalities observed in children treated with HAART is now of major concern.

6.1 Lipodystrophy syndrome (LDS)

Despite difficulties in assessment and the lack of a standardized definition, fat redistribution in LDS is increasingly recognized in children [53]. It is of great concern, because of its potential metabolic consequences and the

Table 9 Summary of suggested routine monitoring of a child on ART

Every 3 months
Height and weight.
Formal adherence questionnaire and pharmacy records check.
Clinical examination for lipodystrophy syndrome.
FBC, electrolytes, liver function tests, calcium, phosphate and alkaline phosphatase (amylase if on ddI).
CD4 count and percentage.
Viral load.
Annual
Tanner pubertal stage.
Fasting blood lipids if on ritonavir boosted PI.
Resistance testing
Resistance testing – infants born to mothers on ART, and all children failing second and subsequent regimens.

impact that body changes may have in self-image leading to poor adherence and treatment failure. The commonest clinical picture seen is facial and limb lipoatrophy, but truncal obesity and buffalo hump also occur, with or without elevations in blood lipid levels. Current cross-sectional studies in paediatric clinics in Europe have reported the prevalence of LDS to range from 2% to 33% as assessed on clinical grounds and anthropometric measurements [19,54–56]. In a large recent European questionnaire survey including 374 children with a median age of 5 years, an overall prevalence of clinical LDS was reported to be 28% [57]. There is a need for longitudinal data on LDS and a substudy of the PENPACT1 trial is on-going.

Several studies in adults have observed abnormalities in fat distribution by dual energy X-ray absorbiometry (DEXA) before clinical signs are recognized [58,59]. DEXA provides accurate information about subcutaneous fat, whereas CT or MRI scanning may be useful to tell between abdominal subcutaneous fat stores of the overweight child and intra-abdominal visceral fat seen in LDS. Risk factors for LDS include puberty, female sex, advanced disease and duration of time on ART. There is an association with PI use, and peripheral lipoatrophy is clearly linked to D4T use, especially if combined with ddI (D4T + ddI combinations should be avoided if at all possible).

In children, hypercholesterolaemia appears to be more common than hypertriglyceridaemia [55,60,61]. RTV-boosted PIs have been most associated with abnormal blood lipids, cholesterol, triglycerides and low density lipoprotein. All children on RTV-boosted PIs including LPV should have fasting blood lipids measured at least annually. Consideration should be given to switching the PI to an NNRTI or abacavir in children with markedly elevated blood lipids [30]. There is very limited experience of statins in children.

6.2 Mitochondrial toxicity

Mitochondrial toxicity may result from therapy with NRTIs, and severe lactic acidosis is a rare but serious toxicity attributed to this class of antiretrovirals. Large prospective adult studies have estimated an incidence of symptomatic hyperlactataemia of 0.4–0.8 per 100-patient-years [62,63]. The predictive value of random lactate determinations is low, suggesting that routine lactate should not be checked in clinical practice in the absence of symptoms [64]. There are also difficulties in determining venous lactate in optimal conditions. Even true hyperlactataemia is usually asymptomatic and may be transient [65]. Isolated case reports of fulminant severe lactic acidosis and death have been seen in children [66]. Treatment with mitochondrial multivitamin rescue can be considered. A high index of

suspicion is necessary for mitochondrial toxicity because early symptoms are non-specific. A special situation occurs in children born to HIV-infected mothers exposed to NRTIs *in utero* in whom the prevalence of transient hyperlactataemia is greater [66], suggesting reversible mitochondrial dysfunction. Although the great majority of children are asymptomatic, these infants may have a slightly higher risk of mitochondrial disorders including neurological dysfunction [67,68].

6.3 Osteoporosis

There have been increasing reports of osteonecrosis and abnormalities of bone mineral metabolism in patients on HAART. Osteonecrosis usually results from circulatory insufficiency, and the areas most often involved are the femoral and humeral heads. A large cross-sectional study using MRI detected avascular necrosis of the hip in 4% of adults, even before clinical symptoms developed [69]. In children, a large case-controlled study has suggested that Legg-Calve-Perthe's disease is nine-fold more frequent in HIV-infected children than in the general population. The incidence of osteopenia and osteoporosis is increased in adults treated with HAART, although the association with PIs is not clear [70–72]. The pathogenesis is not obvious, although decreased bone mineral content may be a result of mitochondrial toxicity (and associated with NRTI use) [73]. An association has been reported between osteopenia in children and ART [74], including duration of time on ART [75].

The consequence of decreased bone mineral density is unknown, but is of great concern due to the fact that the physiologic peak value of bone mass density is achieved in young adults and may be permanently impaired in HIV-infected children as a result of osteopenia, with the subsequent risk of pathological fractures. Although to date reports of bone fractures are rare, observational data from the PACTG 219 study indicate that they may be more common in HIV-infected children [76]. Biphosphonates have demonstrated some benefit in the treatment of osteopenia and osteoporosis in HIV-infected adults [77] and should be considered in children with pathological fractures and severe osteoporosis.

6.4 Diabetes

Altered glucose homeostasis is seen in adult patients treated with HAART. Although fasting glucose levels remain normal in most adults, impaired glucose tolerance and hyperinsulinaemia are not uncommon in PI-treated patients, and the incidence of diabetes mellitus is increased in PI-treated compared with untreated HIV-patients [78]. In

contrast, to date, impaired glucose tolerance has been infrequently reported in children and diabetes is very rare. The true prevalence of insulin resistance is difficult to assess in clinical practice, but may assume greater importance as children remain on HAART for longer periods of time.

A summary of the suggested minimum routine clinical monitoring for a child on ART is given in Table 9. Table 10 summarized prescription and administration information, and Table 11 summarized Toxicities of antiretrovirals.

These guidelines are available on the PENTA website www.pentatrials.org. They will be updated again in 2006.

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Table 10 Summary of prescribing and administration information for antiretrovirals

		Dosage (oral unless specified)						
Names of drug	Nucleoside/Nucleotide reverse transcriptase inhibitors (NRTIs/NRTIs)	Paediatric (Tanner stages 1–3)			Adolescent (Tanner stages 4–5)/adult	Formulations	Special instructions	
		Neonatal (<30 days)	Infant (1–12 months)	Oral				
Zidovudine (ZDV, AZT, Retrovir)	<p>Oral</p> <p>Term: 4 mg/kg b.d. or 2 mg/kg q.d.s.</p> <p>Premature: ≥ 30 weeks: 2 mg/kg b.d. for 2 weeks then 2 mg/kg t.d.s. ≤ 30 weeks: 2 mg/kg b.d. for 4 weeks then 2 mg/kg t.d.s.</p> <p>IV</p> <p>Term: 1.5 mg/kg q.d.s. Premature: 1.5 mg/kg b.d.</p>	<p>Oral</p> <p>1–3 months: 4 mg/kg b.d. or 2 mg/kg q.d.s.</p> <p>IV</p> <p>1–3 months: 1.5 mg/kg q.d.s.</p>	<p>Oral</p> <p>Over 3 months: 360 mg/m²/day in two divided doses</p> <p>Intravenous (IV) infusion</p> <p>Over 3 months: Intermittent: 120 mg/m² q.d.s. or Continuous: 20 mg/m²/h</p>	250–300 mg b.d.	<p>Capsules: 100 mg, 250 mg</p> <p>Tablets combined with lamivudine: Zidovudine 300 mg, lamivudine 150 mg (Combivir)</p> <p>Syrup: 10 mg in 1 mL</p> <p>Infusion: 10 mg in 1 mL, 20 mL vials</p>	<p>Large volume of syrup not well tolerated in older children.</p> <p>Infusion: Dilute with 5% dextrose to a concentration of ≤ 4 mg/mL. Intermittent infusion is given over 1 h</p>		
Didanosine (ddI, dideoxyinosine, Videx)	<p>60 mg/m² b.d. or 100 mg/m² o.d.</p>	<p>Less than 3 months: 60 mg/m² b.d. or 100 mg/m² o.d.</p> <p>Over 3 months: 240 mg/m²/day in 1 or 2 divided doses</p>		<p><60 kg: 250 mg o.d. or 125 mg b.d.</p> <p>≥ 60 kg: 400 mg o.d. or 200 mg b.d.</p>	<p>Capsules: 125 mg, 200 mg, 250 mg, 400 mg (Tablets: 25 mg, 200 mg)</p> <p>Oral suspension: 10 mg in 1 mL</p>	<p>Enteric coated capsules ideally to be taken at least 2 hours before or after food.</p> <p>Tablets: Rarely used in children. To ensure sufficient antacid each dose to be taken as 2 tablets (child under 1 year 1 tablet) chewed, crushed or dispersed in water or clear apple juice.</p> <p>Oral suspension: 1-month expiry. Store in a refrigerator. Ideally taken 1 h before or 2 h after food. May be less important in children.</p> <p>Small tablets. Syrup no longer available.</p>		
Zalcitabine (ddC, dideoxycytidine, Hivid)	Unknown		0.03 mg/kg/day in 2 or 3 divided doses		Tablets: 375 µg, 750 µg			
Stavudine (d4T, Zerit)	Under study: (ACTG332) 1 mg/kg b.d.	Over 3 months and <30 kg: 1 mg/kg b.d. ≥ 30 –60 kg: 30 mg b.d.		<p><60 kg: 30 mg b.d.</p> <p>≥ 60 kg: 40 mg b.d.</p>	<p>Capsules: 15 mg, 20 mg, 30 mg, 40 mg</p> <p>Oral solution: 1 mg in 1 mL</p>	<p>Oral Solution: 1-month expiry. Store in a refrigerator. Large volume of syrup.</p>		

(Continued)

Table 10. (Contd.)

Dosage (oral unless specified)		Paediatric (Tanner stages 1–3)			Adolescent (Tanner stages 4–5)/adult		Formulations		Special instructions	
Names of drug	Neonatal (<30 days)	Infant (1–12 months)	Paediatric (Tanner stages 1–3)	Adolescent (Tanner stages 4–5)/adult	Formulations	Special instructions	Formulations	Special instructions		
Lamivudine (3TC, EpiVir)	2 mg/kg b.d.	Over 1 month: 4 mg/kg b.d. or 8 mg/kg o.d. (PENTA 13). Maximum 300 mg daily.	150 mg b.d. or 300 mg o.d.	Tablets combined with zidovudine – see abacavir and zidovudine – see abacavir Oral solution: 10 mg in 1 mL	Tablets: 100 mg, 150 mg Tablets combined with zidovudine and lamivudine: abacavir 300 mg, zidovudine 300 mg, lamivudine 150 mg (Frizivir) Oral solution: 20 mg in 1 mL	Well tolerated. Use oral solution within 1 month of opening	Tablets: 300 mg Tablets combined with zidovudine and lamivudine: abacavir 300 mg, zidovudine 300 mg, lamivudine 150 mg (Frizivir) Oral solution: 20 mg in 1 mL	Must caution parents about risk of serious hypersensitivity. Patients should not interrupt therapy without consulting their doctor.		
Abacavir (ABC, GW1592U89, Ziagen)	2 mg/kg b.d.	1–3 months: 8 mg/kg b.d. under study. Over 3 months: 8 mg/kg b.d. or 16 mg/kg o.d. (PENTA 13). Maximum 600 mg daily.	300 mg b.d. or 600 mg o.d.	Tablets: 300 mg Tablets combined with zidovudine and lamivudine: abacavir 300 mg, zidovudine 300 mg, lamivudine 150 mg (Frizivir) Oral solution: 20 mg in 1 mL	Capsules: 200 mg Oral solution: 10 mg in 1 mL not available until late 2004.		Capsules: 200 mg Oral solution: 10 mg in 1 mL not available until late 2004.	Because of the lower bioavailability of the oral solution the maximum dose is 240 mg o.d.		
Emtricitabine (FTC, Emtriva)	Unknown. Less than 4 months – no data	Over 4 months: 6 mg/kg o.d.	< 33 kg: 6 mg/kg o.d. to a maximum of 240 mg o.d. as oral solution or 200 mg o.d. as a capsule. ≥ 33 kg: 200 mg capsule o.d.	200 mg capsule o.d.				Liquid formulation not available until late 2004.		
Tenofovir disoproxil fumarate (Viread)	Unknown	Unknown	2–8 years: 8 mg/kg as suspension Over 8 years: 175 mg/m ² o.d. under study (928) < 18 years: 6 mg/kg o.d. under study Maximum 300 mg o.d. Adult: 300 mg o.d.	Tablets: 300 mg Suspension: not available until early 2006.	Tablets: 300 mg	Administer with food to enhance absorption. ddl serum concentrations increased when given with tenofovir. Patients should be monitored for ddl toxicity.	Tablets: 300 mg	tenofovir disoproxil fumarate 300 mg.		

Table 10. (Contd.)

Dosage (oral unless specified)		Non-nucleoside analogue reverse transcriptase inhibitors – (NNRTIs)			Special instructions	
Names of drug	Neonatal (< 30 days)	Infant (1–12 months)	Paediatric (Tanner stages 1–3)	Adolescent (Tanner stages 4–5)/adult	Formulations	
Nevirapine (NVP, Viramune)	Inadequate data but 2–5 mg/kg o.d. has been used. Post Exposure Prophylaxis (combined with 2 NRTIs) 2 mg/kg o.d. for 14 days then stop due to long half-life. Continue NRTIs for 4 weeks in total. If treatment is to continue increase to 4–5 mg/kg o.d. after 14 days and increase again at 2 months	Inadequate data. 150–200 mg/m ² /day o.d. for 14 days then, if no rash, increase to 300–400 mg/m ² /day in 2 divided doses. Alternatively: 2 months–8 years: 4 mg/kg o.d. for 14 days then 7 mg/kg b.d. Maximum 400 mg daily. 8–16 years and < 50 kg: 4 mg/kg for 14 days then 4 mg/kg b.d. ≥ 50 kg: adult dose.	Over 16 years: 200 mg o.d. for 14 days then 200 mg b.d. 400 mg o.d. unlicensed	Tablets: 200 mg Suspension: 10 mg in 1 mL	Few data on use with PI. Practice is to increase PI dose by about 30%. Suspension: Shake well. Store at room temperature.	
Efavirenz (EFV, Sustiva)	Unknown	Inadequate data in children < 3 years or < 13 kg. Capsules: Over 3 years: 13–15 kg, 200 mg o.d. 15–20 kg, 250 mg o.d. 20–25 kg, 300 mg o.d. 25–32.5 kg, 350 mg o.d. 32.5–40 kg, 400 mg o.d. Over 12 years and/or ≥ 40 kg: 600 mg o.d. Oral solution: Over 5 years: 13–15 kg, 270 mg o.d. (9 mL) 15–20 kg, 300 mg o.d. (10 mL) 20–25 kg, 360 mg o.d. (12 mL) 25–32.5 kg, 450 mg o.d. (15 mL) 32.5–40 kg, 510 mg o.d. (17 mL) ≥ 40 kg: 720 mg o.d. (24 mL) 3–< 5 years: 13–15 kg, 360 mg o.d. (12 mL) 15–20 kg, 390 mg o.d. (13 mL) 20–25 kg, 450 mg o.d. (15 mL) 25–32.5 kg, 510 mg o.d. (17 mL) 15 mg/kg o.d. Unknown	600 mg o.d.	Capsules: 50 mg, 100 mg, 200 mg 600 mg Tablets: 600 mg Oral solution: 30 mg in 1 mL	Bedtime dosing is recommended especially during the first 2–4 weeks to improve tolerability of CNS side effects. The bioavailability of Sustiva oral solution is lower than that of the tablets or capsules. Capsules may be opened & added to food. Contents have a peppery taste.	
Delavirdine (DLV, Rescriptor)	Unknown	Unknown	Unknown	400 mg t.d.s. or 600 mg b.d.	Tablets: 100 mg, 200 mg	Rarely used. 100 mg tablets can be dispersed in water or cola and taken promptly. 200 mg tablets are not readily dispersible. Should be taken 1 h before or after ddl or antacids.

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Table 10. (Contd.)

Dosage (oral unless specified)						
Names of drug	Neonatal (<30 days)	Infant (1–12 months)	Paediatric (Tanner stages 1–3)	Adolescent (Tanner stages 4–5)/adult	Formulations	Special instructions
Protease inhibitors (PIs)						
Indinavir (IDV, Crivivan)	Do not use in neonates due to risk of kernicterus	The safety and efficacy of the capsules is not established in children less than 4 years. > 3 months–17 years: 500 mg/m ² t.d.s. Patients with a small surface area may require 300–400 mg/m ² t.d.s. With low dose ritonavir: 2–18 years: Indinavir 350 mg/m ² b.d. with ritonavir 125 mg/m ² b.d.		800 mg t.d.s. With low dose ritonavir: Indinavir 400 mg b.d. with ritonavir 400 mg b.d. Indinavir 800 mg b.d. with ritonavir 100–200 mg b.d.	Capsules: 100 mg, 200 mg, 333 mg, 400 mg	Take on an empty stomach 1 h before or 2 h after a meal (or can take with a light meal). In combination with ritonavir food restrictions do not apply. Adequate hydration is required to reduce risk of nephrolithiasis (at least 2.5 pints in adults). If given with ddl give at least 1 hour apart on an empty stomach. NVP or EFV are likely to reduce IDV levels. Store in original container with desiccant.
Ritonavir (RTV, Norvir)	Under study (PACTG-354) 350 mg/m ² b.d.	Usual dose: 400 mg/m ² b.d. Start with 250 mg/m ² b.d. to minimize risk of nausea and vomiting. Increase stepwise to full dose over 5 days as tolerated. Dose range 350–400 mg/m ² b.d.		600 mg b.d. starting with 300 mg b.d. and escalating over 5 days or more as tolerated. Low dose to boost other PIs: e.g. 100 mg b.d.	Capsules: 100 mg Oral solution: 80 mg in 1 mL	Take with food to increase absorption and reduce gastrointestinal side effects. If RTV is given with ddl there should be 2 h between taking each of the drugs. Oral solution must be kept in the fridge and stored in the original container. Can be kept at room temperature if used within 30 days. To minimize nausea and vomiting escalate dose over 5 days or so as tolerated. Oral solution contains 43% alcohol and is very bitter. Do not mix it with water.

Table 10. (Contd.)

Names of drug	Dosage (oral unless specified)				Formulations	Special instructions
	Neonatal (<30 days)	Infant (1–12 months)	Paediatric (Tanner stages 1–3)	Adolescent (Tanner stages 4–5)/adult		
Sequinavir (SQV, Invirase, Fortovase)	Unknown	Unknown	Under study: 50 mg/kg t.d.s. with nelfinavir: 33 mg/kg t.d.s.	Over 16 years: Fortovase 1.2 g t.d.s. or 1.6 g b.d. With low dose ritonavir: Fortovase 1 g b.d. or Invirase 1 g b.d. with ritonavir 100 mg b.d.	Capsules: 200 mg hard gelatine (Invirase), 200 mg soft, gel-filled (Fortovase)	To increase tolerability: <ul style="list-style-type: none"> • Mix solution with milk, chocolate milk or ice cream. • Dull the taste buds before giving, with ice or lollies. • Coat the mouth with peanut butter before the dose. • Give strong tasting food straight after the dose e.g. cheese, chewing gum.
	Unknown	Unknown				Take within 2 h after a meal. SQV concentration increased by giving with grapefruit juice. Photosensitivity can occur – sunscreen or protective clothing advised. Fortovase and Invirase are not interchangeable.
Nelfinavir (NFV, Viracept)	Under study: 40 mg/kg b.d. (PACTG-353) 50–75 mg/kg b.d. as infant PEP			750 mg t.d.s. 1250 mg b.d.	Tablets: 250 mg, 625 mg Oral powder: 50 mg/g	Take with food to enhance absorption. Can crush tablets and disperse in water then mix with milk / chocolate milk. Crushed tablets can be mixed with food. Do not mix with acidic food or juice due to poor taste. Adolescents need higher doses than adults do. If given with ddI NFV should be given 2 h before or 1 hour after ddI.
		< 1 year: 75 mg/kg b.d. > 1 year: 60 mg/kg b.d.				

(Continued)

Table 10. (Contd.)

Dosage (oral unless specified)		Paediatric (Tanner stages 1–3)		Adolescent (Tanner stages 4–5)/adult		Formulations	Special instructions
Names of drug	Neonatal (<30 days)	Infant (1–12 months)	Paediatric (Tanner stages 1–3)	Adolescent (Tanner stages 4–5)/adult	Formulations		
Lopinavir/ritonavir (LPV/r, Kaletra)	No data on dosing for children <6 months old	6 months–12 years All doses given b.d. with food Weight (kg) 7–<15 15–40 >40 Equivalent to:	Lopinavir/ritonavir dose (mg/kg) No NVP or EFV 12/3 10/2.5 3 capsules i.e. 400 mg/100 mg 230/57.5 mg/m ² BD	Without NVP or EFV: 400/100 mg (3 capsules or 5 mL) b.d. With NVP or EFV: 533/133.3 mg (4 capsules or 6.67 mL) b.d. Lopinavir/ritonavir dose (mg/kg) With NVP or EFV or ↓ susceptibility 13/11.25 11/2.75 4 capsules i.e. 533 mg/133.3 mg 300–133.3 mg/m ² BD	Capsules: lopinavir 133.3 mg with ritonavir 33.3 mg Oral solution: lopinavir 80 mg with ritonavir 20 mg in 1 mL	Higher doses used with NNRTIs or if previously PI experienced. Liquid formulation has a low volume but a bitter taste. Capsules are large. Take with food to enhance absorption – especially the liquid. Store in the fridge. Can be kept at room temperature for 6 weeks. ddl should be taken 1 h before or 2 h after LPV/r. 5 mL oral solution = 3 capsules.	
Amprenavir (APV, Agenerase)	The safety and efficacy of the capsules is not established in children less than 4 years. The oral solution is not recommended under 4 years.		Capsules: Over 12 years and >50 kg: 1.2 g b.d. Over 12 years and <50 kg: 20 mg/kg b.d. Over 4 years: 20 mg/kg b.d. Maximum 2.4 g daily. With low dose ritonavir: Over 12 years and >50 kg: Amprenavir 600 mg b.d. with ritonavir 100–200 mg b.d. or Amprenavir 1200 mg o.d. with ritonavir 200 mg o.d. Oral solution: Adult and child >4 years: 17 mg/kg t.d.s. or 22.5 mg/kg b.d. Maximum 2.8 g daily.		Capsules: 50 mg, 150 mg Oral solution: 15 mg in 1 mL	The bioavailability of the oral solution is 14% lower than the capsules. The formulations are not interchangeable on a mg-for-mg basis. Oral solution has low volume but bitter taste. It contains propylene glycol and an extremely high dose of vitamin E. 150 mg capsules are very large; alternatively many small 50 mg capsules have to be taken. APV should be taken at least 1 h before or after antacid or ddl.	
Fosamprenavir	Unknown. Not approved in children. Phase I/II underway (APV 20002 and 20003).			With low dose ritonavir: fosamprenavir 700 mg b.d. with ritonavir 100 mg b.d.	Tablets: 700 mg		

Table 10. (Contd.)

Dosage (oral unless specified)						
Names of drug	Neonatal (<30 days)	Infant (1–12 months)	Paediatric (Tanner stages 1–3)	Adolescent (Tanner stages 4–5)/adult	Formulations	Special instructions
Atazanavir	<3 months: do not use due to risk of kernicterus. Unknown, Phase I/II underway (PACTG-1020A) 4–13 years: atazanavir 400 mg o.d. with low dose ritonavir 100 mg o.d. has been used.			> 13 years: atazanavir up to 600 mg o.d. has been used. Adult: 400 mg o.d. With low dose ritonavir: > 13 years: atazanavir 300–400 mg o.d. with ritonavir 100 mg o.d. has been used. Adult: atazanavir 300 mg o.d. with ritonavir 100 mg o.d.	Capsules: 100 mg, 150 mg, 200 mg	Should be taken with food to enhance absorption. Atazanavir should be taken at least 1 h before or after antacid or ddi.
Tipranavir	Unknown	Unknown	Under study (PACTG-1051 Phase I/II) 2–18 years: tipranavir 290 mg/m ² b.d. with ritonavir 115 mg/m ² b.d. or tipranavir 375 mg/m ² b.d. with ritonavir 150 mg/m ² b.d. With low dose ritonavir: ≥ 13 but < 18 years plus weight ≥ 50 kg: tipranavir 500 mg b.d. with ritonavir 200 mg b.d. (i.e. adult dose).		Capsules: 250 mg	Tolerance improved by taking with food.
Fusion inhibitors						
Enfuvirtide (T20, Fuzeon)	Not approved for use in paediatric patients below 6 years of age due to lack of data. 6–16 years: 2 mg/kg b.d. Maximum 90 mg (1 mL). Doses under study: (given b.d.) (PACTG-1005)					
	Weight (kg)	Dose/Injection (mg)	Volume (ml) of 90 mg in 1 mL solution			
11.0–15.5	27	0.3				
15.6–20.0	36	0.4				
20.1–24.5	45	0.5				
24.6–29.0	54	0.6				
29.1–33.5	63	0.7				
33.6–38.0	72	0.8				
38.1–42.5	81	0.9				
≥ 42.6	90	1.0				
	Injection: 108 mg of enfuvirtide powder for injection when reconstituted with 1.1 mL water for injection to deliver: enfuvirtide 90 mg in 1 mL. Can take up to 45 min to dissolve. Once reconstituted it should be injected at once or kept refrigerated in the original vial until use. Must be used within 24 h. Injected subcutaneously in to the upper arm, anterior thigh or abdomen.					

Table 11 Summary of the major toxicities of antiretrovirals

Names of drug	More common side effect	Less common (more severe)	Rare
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/NNRTIs)			
Zidovudine (ZDV, AZT, Retrovir)	Haematologic toxicity including anaemia and granulocytopenia. Headache, nausea.	Myopathy, myositis and liver toxicity.	Unusual (severe): cases of mitochondrial toxicity have been reported (Section 6.2). Some of these have been fatal.
Didanosine (ddl, dideoxyinosine, Videx)	Diarrhoea, abdominal pain, nausea, vomiting.	Pancreatitis (dose related, less common in children than adults). Cases of mitochondrial toxicity have been reported (Section 6.2). Some of these have been fatal.	Peripheral neuropathy (dose related), electrolyte disturbances and hyperuricaemia. Increased liver enzymes and retinal depigmentation.
Zalcitabine (ddC, dideoxycytidine, Hivid)		Peripheral neuropathy, pancreatitis (rare in children), hepatic toxicity, oral ulcers, oesophageal ulcers, haematologic toxicity and skin rashes. Cases of mitochondrial toxicity have been reported (Section 6.2). Some of these have been fatal.	
Stavudine (d4T, Zerit)		Peripheral lipodystrophy as part of Lipodystrophy syndrome (LDS). Peripheral neuropathy. Cases of mitochondrial toxicity have been reported (Section 6.2). Some of these have been fatal.	Increased liver enzymes
Lamivudine (3TC, Epivir)		Pancreatitis (mainly seen in children with advanced HIV infection receiving many other medications). Cases of mitochondrial toxicity have been reported (Section 6.2). Some of these have been fatal.	
Abacavir (ABC, GW1592U89, Ziagen)		Approximately 1–3% of children develop a potentially fatal hypersensitivity reaction. Symptoms include fever, fatigue, malaise, nausea, vomiting, diarrhoea and abdominal pain or respiratory symptoms e.g. shortness of breath. Physical findings include lymphadenopathy, ulceration of mucous membranes and maculopapular or urticarial skin rash. Hypersensitivity can occur without a rash. Laboratory abnormalities include elevated liver function tests, increased creatine phosphokinase and lymphopenia. Most common in first 6 weeks of therapy. In patients with suspected hypersensitivity Abacavir should be stopped. Do not rechallenge as hypotension and death have occurred on re-challenge. Cases of mitochondrial toxicity have been reported (Section 6.2). Some of these have been fatal.	
Emtricitabine (FTC, Emtriva)		Headache, diarrhoea, nausea, rash and skin discoloration (hyperpigmentation on palms and/or soles, predominantly seen in non-Caucasian patients). Cases of mitochondrial toxicity have been reported (Section 6.2). Some of these have been fatal.	

(Continued)

Table 11. (Contd.)

Names of drug	More common side effect	Less common (more severe)	Rare
Tenofovir disoproxil fumarate (Viread)	Evidence of tubular leak syndrome i.e. renal toxicity including increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia and/or calcuria and decreases in serum phosphate have been seen. Hypophosphataemia in > 10%. Patients at risk of renal impairment should be monitored closely.	Approximately 1% discontinued due to gastrointestinal side effects.	At high doses tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals. These effects have not been seen in adults taking tenofovir for up to 1 year. It is unknown if these effects will occur in the longer term or in children. Cases of lactic acidosis and severe hepatomegaly with steatosis have been reported with use of the nucleoside analogues. Some of these have been fatal.
Non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs)			
Nevirapine (NVP, Viramune)	Skin rash in 10%. If mild and systemically well can sometimes treat through with antihistamines. Some are severe requiring hospitalisation. Can be life threatening including Stevens-Johnson syndrome, toxic epidermal necrolysis, fever, nausea, headache and abnormal liver function tests.	Hepatitis which may rarely lead to severe and life-threatening and in some cases fatal liver damage. Very rarely – liver failure and granulocytopenia. Hypersensitivity reactions including, but not limited to severe rash or rash with fever, blisters, oral lesions, conjunctivitis, facial oedema, muscle or joint aches, general malaise and/or significant hepatic abnormalities.	Manufacturers recommend frequent monitoring of LFTs for the first 3 months. The risk of hepatic events is greatest in the first 6 weeks but the risk continues past this period and monitoring is recommended throughout treatment.
Efavirenz (EFV, Sustiva)	Skin rash, CNS system (somnolence, insomnia, abnormal dreams, 'Spacey kids', confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalisation, hallucinations, euphoria). Best avoided if previous psychological problems.		Teratogenic in primates (use in pregnancy should be avoided).
Delavirdine (DLV, Rescriptor)	Headache, fatigue, gastrointestinal complaints and rash (may be severe).		
Protease inhibitors (PIs)			
Indinavir (IDV, Crixivan)	Nausea, abdominal pain, headache, metallic taste, dizziness and asymptomatic hyperbilirubinaemia (10%).	Renal stones/nephritis (4%) and exacerbation of chronic liver disease. Lipodystrophy Syndrome (section 6.1)	Hyperglycaemia, ketoacidosis, diabetes and haemolytic anaemia.
Ritonavir (RTV, Norvir)	Nausea, vomiting, diarrhoea, headache, abdominal pain and anorexia.	Circumoral paresthesias and increases in liver enzymes. Lipodystrophy syndrome (section 6.1).	Pancreatitis, hyperglycaemia, ketoacidosis, diabetes and hepatitis.
Saquinavir (SQV, Invirase, Fortovase)	Diarrhoea, abdominal discomfort, headache, nausea, paresthesias and skin rash.	Lipodystrophy syndrome (section 6.1).	Hyperglycaemia, ketoacidosis and diabetes.
Nelfinavir (NFV, Viracept)	Diarrhoea (mild – moderate)	Abdominal pain. Lipodystrophy syndrome (section 6.1).	Hyperglycaemia, ketoacidosis and diabetes.
Lopinavir/ritonavir (LPV/r, Kaletra)	Diarrhoea, nausea and vomiting.	Lipodystrophy syndrome (section 6.1).	Pancreatitis, hyperglycaemia, ketoacidosis, diabetes and hepatitis.
Amprrenavir (APV, Agenerase)	Vomiting, nausea, diarrhoea, perioral paresthesias and rash.	Life-threatening rash including Stevens-Johnson syndrome in 1% of patients. Lipodystrophy syndrome (section 6.1).	New onset diabetes mellitus, hyperglycaemia, exacerbation of pre-existing diabetes mellitus, haemolytic anaemia.
Fosamprenavir	In adults diarrhoea, nausea, vomiting, abdominal pain and flatulence, headache, hypertriglyceridaemia and rash occurred commonly i.e. 1–10%.	Life-threatening rash including Stevens-Johnson syndrome in < 1% of patients. Lipodystrophy syndrome (section 6.1).	New onset diabetes mellitus, hyperglycaemia, exacerbation of pre-existing diabetes mellitus, haemolytic anaemia.
Atazanavir	Asymptomatic elevations in unconjugated bilirubin (30% patients), jaundice (10% patients) headaches, fever, arthralgia, depression, insomnia, dizziness, nausea, vomiting, diarrhoea and paresthesias.	Prolongation of PR interval on ECG.	Pancreatitis, hyperglycaemia, ketoacidosis, diabetes and hepatitis.

(Continued)

Table 11. (Contd.)

Names of drug	More common side effect	Less common (more severe)	Rare
Tipranavir	In adults diarrhoea, nausea, fatigue, headache and vomiting are common.	Lipid abnormalities and hepatotoxicity.	
Fusion inhibitors			
Enfuvirtide (T20, Fuzeon)	98% patients get local injection site reactions including pain and discomfort, induration, erythema, nodules and cysts, pruritis and ecchymosis. Usually mild or moderate in severity but can be more severe.	Unclear association with an increased rate of bacterial pneumonia.	Hypersensitivity reactions including fever, nausea and vomiting, chills, rigors, hypotension, elevated liver transaminases. Immune-mediated reactions including primary immune complex reaction, respiratory distress, glomerulonephritis and Guillan-Barre syndrome. Therapy should not restart following signs and symptoms consistent with hypersensitivity reactions.