

PENTA guidelines for the use of antiretroviral therapy in paediatric HIV infection

PENTA Guidelines on paediatric ART

Dr Mike Sharland^{1*}, Dr. Guido Castelli Gattinara di Zub², Dr. Jose Tomas Ramos³, Dr Stephane Blanche⁴, Dr Diana M Gibb⁵

¹Paediatric Infectious Diseases Unit, St George's Hospital, London, UK. ²Reparto Malattie Infettive, Ospedale del Bambino Gesù, Roma, Italia. ³Unidad de Inmunodeficiencias Hospital Materno Infantil, Madrid, Espagna. ⁴Service d'Immuno-Hematologie Pediatrique Hôpital Necker Enfants Malades, Paris, France. ⁵Medical Research Council, Clinical Trials Unit, London, UK.

On behalf of the PENTA Steering Committee *

Abstract

Objective: To produce European Guidelines for the use of antiretroviral therapy (ART) in HIV infected children. **Design:** Systematic literature review using Medline, the major antiretroviral conference reports, and IDSA recommendations on guideline production. **Setting:** Paediatric European Network for Treatment of AIDS (PENTA) Steering Committee. **Outcome measure:** Guidelines have been produced for the use of antiretroviral therapy in HIV infected children in Europe. Recommendations on when to start ART, which ART to start, with dosages and a summary of the relevant literature have been produced. **Conclusions:** These guidelines are aimed at assisting paediatricians in Europe with ART prescribing, and provide a more cautious approach to starting therapy than current paediatric US guidelines.

Key words: paediatric, antiretroviral therapy, guidelines

Introduction

These guidelines update the previous PENTA paper, written in 1999 (1). In Europe, paediatric dual combination therapy was introduced around 1996-7, followed by protease inhibitor (PI) based triple therapy in 1997-8, and non-nucleoside reverse transcriptase (NNRTI) based triple therapy in 1999-2000. A number of trials have documented dramatic improvements in the surrogate markers of disease progression, viral load (VL), and CD4 lymphocyte count, in children with HIV infection following the introduction of highly active antiretroviral therapy (HAART) (2,3). Other smaller studies have noted a resolution of HIV-related organ disease with HAART (4). Data from both European and North American observational cohort studies have found a marked reduction in the overall mortality of children with HIV associated with the introduction of combination ART (5-7).

However more recently there has been recognition of the problems associated with the introduction of HAART. In adults the metabolic complications (lactic acidosis, lipodystrophy, glucose metabolism, osteopenia) are well

described, and similar changes are now being described in children (8).

Unpalatable drug formulations and limited pharmacokinetic data in children have contributed to difficulties in prescribing HAART to young children, and long term adherence is very difficult for families. Complex social needs and family illness compounds these problems. In adults, the difficulties of maintaining good long term adherence, and greater recognition of drug toxicity have led to more conservative attitudes to starting early HAART; most recent European and North American adult guidelines now recommend delaying use of HAART until the patients' CD4 cell count has fallen to 200-350 (9)(10).

The aim of these PENTA guidelines is to assist paediatricians in prescribing antiretroviral therapy (ART) in Europe (11). They take account of other national European guidelines (12,13), and might be read alongside the North American paediatric antiretroviral guidelines (14). This document does not aim to repeat the excellent other guidelines available, but provides another viewpoint from the available evidence. It has been based on a systematic review of the literature using Medline, the major antiretroviral conference reports and IDSA recommendations on guideline production (15). The document reflects the views of the PENTA Steering

Dr Mike Sharland, - Corresponding author ¹Paediatric Infectious Diseases Unit, 5th Floor, Lanesborough Wing, St George's Hospital, Blackshaw Road, London SW17 0QT, UK. Tel/Fax 020 8725 3262, email mike.sharland@stgeorges.nhs.uk

Committee. Because of the complexity of current ART regimens, the PENTA Steering Committee believes that children with HIV should be cared for in collaboration with a specialist paediatric HIV centre.

Background

1). Despite being infected with a potentially lethal virus, not all children with HIV require ART when first seen. Although early cohort studies reported 20% progression to AIDS or death in infancy, they also reported that 40-50% of vertically infected children survived to around 10 years of age without ART (16-18). A few children with long term non-progressive disease may not require ART until adolescence or early adult life.

2). Although the clinical outcome following the introduction of HAART in children is excellent, with dramatically reduced mortality reported from various cohorts, the eradication of HIV from infected adults or children is not possible with the currently available drugs (19,20). Although the ultimate goal of therapy in previously ART untreated (naïve) patients must be to maximally reduce viral replication by decreasing plasma viral load below the limit of detection (<50 copies/ml) to prevent the selection of drug resistant strains, in many naïve and especially in ART experienced children, this goal cannot be achieved. In practice, the current aim of therapy is to maintain the immunological status that prevents clinical disease progression.

3). Difficulties in achieving adequate long-term adherence to HAART represents a major barrier to obtaining a good response. The timing of initiating therapy and the choice of drugs must be influenced by the likelihood that the child will take them. Regular assessment of adherence is very important, and more formal measurements of adherence (e.g. questionnaires, MEM caps) are entering routine clinical care. Poor family social circumstances compound the adherence difficulties, and careful social assessment and plans for family support should always precede starting therapy.

4). Immune reconstitution differs in children compared with adults. Most children treated with HAART have excellent immune repopulation and treatment very early in life following mother to child transmission may be associated with better immune reconstitution (21). In children, the CD4 response to HAART is predominantly CD4 naïve cells. These are newly derived from the thymus, which is still very active in children (22,23). In adults, immune recovery appears to be independent of the baseline CD4 count as long as HAART is started before it falls below 200. Similarly, CD4 responses have been reported to be greatest in children with the lowest CD4% before starting HAART (24).

However, there are no data to show early treatment is associated with an improved long-term clinical outcome. It is therefore still not clear whether the potential virological and immunological benefits in starting HAART early in children, outweigh the problems with adherence, resistance, and toxicity. In asymptomatic infants, the theoretical advantage of treating a primary infection has to be weighed against the added major pharmacokinetic difficulties.

5). Viral load reduction following the introduction of HAART may be slower in children compared to adults, taking a longer time to reach an undetectable VL (25, 26). In both trials and cohort studies, children are starting from a higher viral load than adults at similar stages of disease progression. This higher baseline VL seen in children may be one reason why children less commonly achieve an undetectable VL (UVL) (26). The proportion of children achieving a VL of <400 copies/ml, following the introduction of HAART is commonly under 50% (27). However, care must be taken when interpreting older cohort data. With more recently available drugs, the degree of response may be significantly improved (28).

6). The limited studies of HAART in children suggest that broadly similar improvements are seen in surrogate markers with many different ART regimens. Therefore the availability of a suitable formulation, and the simplicity of the dosage schedule should in large part determine the initial choice of ART. Consideration should also be given to minimising toxicity and cost, and take into account previous ART history. Drug interactions are a major problem with ART, and all other medications must be reviewed. Monitoring peak and trough drug levels may be useful when drug interactions are likely.

7). Many children in Europe and North America are currently ART-experienced and have developed virological failure, but without immunological or clinical progression. There are limited data available on when to change therapy, which subsequent regimens are optimal, and the role of resistance assays. Paediatricians may opt to delay changing therapy in clinically well children with stable CD4% in the presence of virological failure (defined as HIV RNA VL not achieving levels <50 copies/ml, or increasing 1 log above nadir). This strategy implicitly accepts that increasing numbers of resistance mutations may develop over time. Changing ART regimens is frequently determined by the availability of new antiretrovirals. It is likely that children will continue to move to new ART regimens as they develop resistance or toxicity with their current therapy, and new drugs become available. The concept of salvage therapy should be limited to children with clinical, immunological, and virological failure. For most children the aim is to preserve the child's immunological status and clinical

well being. The role of immunotherapy and structured treatment interruptions in children requires further evaluation in clinical trials.

When to Start ART

The PENTA 1 trial of early versus deferred zidovudine (29) remains the only randomised trial addressing the issue of when to start ART in children, and showed no benefit from starting zidovudine monotherapy early compared with starting when symptoms had developed. There are no trials in adults or children addressing the question of when to start combination antiretroviral therapy and recommendations at present can only be made based on analyses from cohort data of the predictive value of surrogate markers in the absence of therapy, as well as data on the response to ART in adults and children.

All recommendations based on surrogate marker data should be seen as a continuum. Emphasis should be placed on **serial** CD4 percentage, VL and clinical assessment. Progressive immunological and growth failure are of particular concern. Starting ART is rarely an emergency. Viral load and CD4% can fluctuate, and at least two or three values should be obtained. Time spent on preparing and educating the family before commencing ART is never wasted. Starting ART must be an informed positive decision by the family if it is to succeed. Start in haste – repent at leisure! Older children commencing ART should know why they are taking treatment, with either full or partial disclosure.

Consideration of when to start ART is based on the available knowledge of predictors of progression to AIDS and death. We consider the clinical, immunological and virological predictors of disease progression separately for infants and for older children. Recommendations are shown in Table 2.

A). Infants

1). Clinical Stage

Infants who present with clinical AIDS have a very poor outcome unless treated with HAART.

All infants presenting with Clinical stage C disease should start HAART as soon as treatment of their AIDS defining illness permits.

2). CD4 and viral load data

In asymptomatic infants, current surrogate markers are not specific enough to predict the slower progressors who may remain asymptomatic for over 5 years without ART, and those who will develop more rapidly progressive disease. High viral loads and low CD4% are

both independent predictors of disease progression in infants, but are of low predictive value for an individual child (30). Infants have a substantial risk of developing AIDS even with high CD4 values.

The widespread uptake of antenatal testing has resulted in fewer infants presenting with rapid progressive disease, but also the early identification of small numbers of infected infants in the pre-symptomatic stage. The limited experience of treatment with 3 or 4 drugs initiated in the first months of life leading to undetectable VL and apparently normal immune function, supports the idea of treating infants as early as possible. It is theoretically possible that early therapy during primary infection may change the long-term outcome of the disease (31). However there are concerns about the lack of HIV specific immune responses reported - most likely due to absence of HIV antigen presentation, and the problems of resistance and toxicity in ART treated infants who fail to achieve complete viral suppression (21).

B). Children

1). Clinical stage

Analysis of the CDC clinical staging system has reported that Stage C (AIDS) is a good predictor of a poor clinical outcome, but clinical stage B disease includes conditions with different predictive value (32). All children with clinical stage C disease should start ART as a matter of urgency.

2). Immunological stage

In normal children, CD4 cell count decreases with age, and CD4 percentage is the better marker (although this decreases with age in very young children). Data on disease progression based on surrogate markers are limited in children and are summarised in Table 1 (14,30,33). However, a recent meta-analysis of over 3000 untreated children from cohorts and trials in Europe and US showed that for children aged >2 years, the 12-month risk of developing AIDS was approximately constant at around 6% for CD4 \geq 20%, but rose sharply at CD4 below 20% (34). Similarly the annual risk of death increased sharply from < 2% for CD4 \geq 10% to greater than 10% at CD4=5%. For children aged 1-2 years, thresholds were similar but the risks were higher (34).

3). Viral Load data

HIV RNA viral load is very high in infants following primary infection and slowly declines over years in the absence of treatment. Over 6 months of age, the risk of progression to AIDS or death increase sharply for VL values above 10^5 copies/mL. In the meta-analysis discussed above, at 2 years of age the risk of progressing

to AIDS was about 5% at a VL <10⁵ copies/mL but over four times higher at VL > 10⁶ copies/mL (34).

Which ART to Start

There has been very few randomised paediatric trials of HAART that provide direct comparisons of different regimens. Most data comes from company sponsored non-randomised studies. It is difficult and may be misleading to directly compare outcome data from different studies where age, disease stage, CD4 and VL, and ART experience differ at baseline. Many abstracts and papers do not provide key surrogate marker outcome data. Therapeutic decisions are often largely based on tolerability of the drugs. Discussion with families should include the taste and volume of syrups, pill size, numbers, and crushability, any storage and food requirements, immediate (nausea/ vomiting/diarrhoea) and late side effects.

Infants

Treatment in infants is complex. Both drug absorption and metabolism are different in infants, and very high doses (particularly of PI drugs) may be required to achieve adequate drug levels. Maternal antiretroviral therapy and the possibility of vertical transmission of drug resistant virus need to be considered. There are three main recent studies of PI therapy in infants. Zidovudine, lamivudine and ritonavir was studied in 39 infants by Chadwick, with 60-70% achieving a VL <400 by 48 weeks (35).

Data on nelfinavir in combination with d4T and ddI has been reported on the first 16 infants in the PENTA 7 trial. Only 50% had a VL <400 copies/ml by week 24 despite most infants receiving 150 mg/kg/day (a dose shown to be necessary in a sub study)(36). A further 24 infants receiving NFV were studied by Capparelli (37), with a very variable PK noted, and an overall lower absorption of nelfinavir than seen in older children. Smaller studies have reported observations on responses to triple nucleosides (38) (39). The option of AZT + 3TC + ABC with NVP (added after one month to minimise possible confusion between ABC hypersensitivity and NVP rash) is an attractive combination that needs further study (40).

Children

1). Protease Inhibitor (PI) based regimens

The PACTG 338 trial compared a PI (Ritonavir) containing regimen (with NRTI backbones of ZDV+3TC or d4T) with dual NRTI alone in children who had previously received NRTI therapy, and the PI regimens had superior CD4 and VL responses compared with the dual NRTI regimen. However, although the volume of

RTV was low, the unpleasant taste and poor GI tolerability are major barriers to using this drug in children (41).

The PACTG 377 trial, also in previously NRTI treated children, showed similar responses in children receiving NFV or RTV based triple regimens, but a higher proportion of children responded if they received a 4-drug regimen including all 3 classes of drugs (NFV, NVP and 2 NRTI) (42). Overall, the PACTG 338 and 377 trials reported that approximately 40-50% of children receiving 2 NRTI's and ritonavir or nelfinavir achieved plasma HIV-1 RNA <400 copies/ml at 24 weeks.

In the PENTA 5 trial which compared dual NRTI combinations of ZDV, 3TC and ABC with or without NFV in 128 previously untreated children, overall 64% of children attained VL <400 copies/ml (despite about 20% of children being only on 2 drugs). Previous NRTI exposure may be the reason for the lower response rates in the PACTG trials, although in both, children had higher CD4% and lower HIV RNA at baseline than in PENTA 5. PENTA 5 was the only trial to compare NFV with placebo but was powered only to compare toxicity between the 2 groups. Diarrhoea was more common in the NFV group but was mild and did not result in drug discontinuation. NFV powder was very poorly tolerated and nearly all children switched to crushed tablets, although pill burden was high for older children (2). Similar results were obtained when nelfinavir was studied combined with dual NRTI, showing crushed tablets to be well tolerated, with diarrhoea the main side effect (43).

In a non-randomised study in previously NRTI treated children, nelfinavir and efavirenz were combined with an NRTI (3). At 48 weeks, the proportion with plasma HIV-1 RNA <400 copies/ml was 76%, and 63% had values <50 copies/ml. However the median HIV RNA at baseline was only 10,000 copies/ml and high baseline plasma HIV-1 RNA was significantly associated with a decreased likelihood of VL becoming undetectable during treatment. Good responses have been reported using indinavir, with close monitoring of drug levels (44), but the principle problems are the very variable absorption, the poor formulation, and high rate of nephrolithiasis. Saquinavir soft gel alone has very poor pharmacokinetics (45). The early data from amprenavir showed poor surrogate marker response and the current formulation for children is poor, with toxic PEG levels found in children < 4 years (46). Studies of the prodrug of amprenavir are underway. Most recently, data from an open-label study of the PI lopinavir with ritonavir boosting, in combination with 2 NRTI have been presented. A total of 100 children (44 ART naïve and 56 previously treated with PI and NRTI's) were followed for 48 weeks. In an Intention To Treat analysis, the

proportion achieving HIV RNA <400 copies/ml by 48 weeks was 84% in naïve and 75% in pre-treated children (71% and 63% respectively had <50 copies/ml) (28). Pharmacokinetic studies of this drug are now being undertaken in children less than two years of age.

2). Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI) based regimens

Excellent results have been reported in adults using NNRTI's as first line therapy (10). Because of the major concerns with metabolic toxicity associated with PI use, many adult specialists now routinely use an NNRTI based combination as their standard first regimen. There are very few data on NNRTI based triple regimens without a PI in children. The principle study of nevirapine was ACTG 245 in NRTI pretreated children, and the 48-week data for ZDV/ddI/NVP combination showed only a 0.3 log VL reduction (47). Although no recent data is available, it is possible this poor response is related to NRTI pre-treatment, dosing, and early development of nevirapine resistance. Cohort data on 74 children treated with HAART including nevirapine (but no PI) from the UK demonstrated that 40% had a VL <400 copies/ml at 24 weeks in ART experienced children, and 60% in ART naïve. There was a dose related response with children treated with higher doses (>300 mg/m²/day) clearly having an improved outcome. A rash was seen in 20%, but in only 5% was this grade 3 or 4 (48). The principal efavirenz study, PACTG 382, combined efavirenz with nelfinavir (3). Good surrogate marker responses were observed (see above) although there are concerns about subsequent regimen options for children who fail a combination including both a PI and NNRTI. The importance of obtaining adequate drug levels for both NFV and EFV was noted, emphasising the importance of therapeutic drug monitoring in children where drug interactions are possible (49). Other cohort studies have reported good surrogate marker data with EFV based regimens, with CNS side effects being the main problem (50) (51).

3). Triple NRTI Regimens

Abacavir combined with 1 or 2 NRTI's has been studied in both naïve and experienced children (52). In the PENTA 5 trial, ABC-containing arms (with ZDV or 3TC) with or without NFV were superior to ZDV+3TC after 24 weeks, and by 48 weeks the ABC+3TC arm had a VL nearly 1 log lower than the ZDV+3TC arm. ABC+3TC was well tolerated and may be a useful backbone for triple therapy in children as identical volumes of each drug can be given twice daily. Resistance studies showed that phenotypic resistance to ABC only developed slowly after the development of 2 or more mutations. Abacavir hypersensitivity was observed in 2 (2%) of children and occurred, as in adults, in the first month of therapy (2).

The triple nucleoside combination most investigated in adults is AZT + 3TC + ABC. There was early concern from adult studies about a poorer outcome in adults treated with triple nucleoside combinations including abacavir, if they had very high VL or advanced AIDS. However 48 week results from CNA 3014 show a similar response to abacavir and indinavir for adults with VL > 5 log copies/ml at baseline (53). In adolescents, Trizivir (containing AZT + 3TC + ABC in 2 tablets a day) can be a very popular option. More data on triple nucleoside combinations are needed in children with advanced disease. Dual nucleoside regimens are still used, mainly in children who commenced dual NRTI in the pre-HAART era and remain very stable.

Recommendation on which ART to Start

See Table 3 for Recommendations, and Table 4 for details of dosages and side effects.

Currently the HAART regimen with most information in paediatrics includes 2 NRTI's plus a PI. From the available data nelfinavir is the most studied PI, however the early data from lopinavir/r are very promising. The role of a triple NRTI based initial regimen requires further investigation in children. There is also an urgent need for more paediatric data on 2NRTI + NNRTI as an initial regimen with a direct comparison to 2 NRTI + PI. The adult data showing surrogate marker similarity between PI and NNRTI- based regimens, and concern about PI related toxicity, has led many paediatricians to use an NNRTI based combination as their routine first line therapy. There are fewer ART naïve children now commencing therapy, emphasising the importance of the new paediatric Penpact1 study, which plans a direct comparison of PI and NNRTI based initial regimens.

Other Issues

Therapeutic Drug Monitoring

There is considerable variation in drug levels achieved even when using standard ART doses for size. The role of therapeutic drug monitoring (TDM) has not been clearly defined for PI and NNRTI therapy in paediatrics but is being increasingly undertaken and requires further research. Intracellular levels of NRTI's are probably more important, and plasma levels may not be useful. TDM is being used both to optimise drug levels, and to monitor adherence. Currently TDM is only definitely indicated where there is the possibility of drug interactions through cytochrome P450 metabolism.

Adherence

It has become very clear from adult and paediatric studies that adherence is one of the principal

determinants of both the level and duration of virological suppression (54, 55). In one recent study, children whose caregivers reported no missed doses in the previous week, were more likely to have an UVL (50% vs 24%) (56).

Watson et al have studied 72 children started on HAART, and related outcome to adherence measured by pharmacy records. A VL < 400 was noted in 52% of adherent children vs 10% in non-adherent (57). Other cohort studies have reported rates of non-adherence when measured by questionnaire of at least 50% (58,59). The reasons are complex and multifactorial. Adherence is difficult to assess in the clinic. No paediatric intervention trial aimed at improving adherence has been conducted. Whenever possible all ART drugs should be given as once or twice daily regimens.

Changing Therapy

Even with an excellent clinical and immunological response observed in most children on HAART, selection of resistant strains is likely to occur in the absence of maintained complete viral suppression. There are concerns that virological failure may lead to immunological and subsequent clinical progression. Despite this, many paediatricians currently delay changing therapy if the child has no sign of clinical or immunological progression. Families and doctors often wish to continue the current regimen when the child is clinically and immunologically stable, and there is not an obvious easy palatable regimen to switch to. The choice of the new regimen will depend on the prior ART history, drug toxicity, availability of new drugs, and if available, guided by resistance testing (60). A clinical trial to evaluate the role of resistance testing is currently ongoing in Europe (PENTA 8, PERA). The Penpact1 trial will evaluate the long-term effects of switching ART at low (>1000 copies/ml) compared with high levels (>30,000 copies/ml) of virological failure.

PACTG 366 is a large paediatric salvage study, where 201 children, approximately half of whom were PI experienced, with an average VL >50,000, and CD4<15% were changed to a 4 drug regimen including 2 or more new drugs. At 48 weeks the VL was <400 in 37% of PI naïve children, compared to 7 % of PI experienced children. Children with a higher baseline CD4% had a better response (61). A small study (11 children) of dual PI use (62) following experience with a single PI regimen showed an average VL reduction of around 1 log, and no children had an UVL at 24 weeks. In a Brazilian cohort study of 95 children (71 % ART experienced) given a new HAART regimen, only 9 (around 10%) achieved a sustained UVL, but a CD4 increase to > 25% was seen in 70% (63). More recent data using Lopinavir/r in PI experienced children, showed that over 50% of children achieved an UVL (28), although these children were also receiving both a NRTI and a NNRTI. Whether or not to switch as soon as viral load rises (to >1000 copies/ml) or

to wait until VL is higher (>30,000 copies/ml) will be addressed in the forthcoming Penpact 1 trial.

Salvage therapy

There are few data on the role of mega HAART in children, where 5 or more drugs from all classes are used together. Strategies include dual PI or dual NNRTI based combinations, possibly combined with IL-2. The principals include optimising adherence, trying to change at least 2 drugs and measuring drug levels because of complex drug interactions if possible. However the risk of poor adherence and drug toxicity is high, and an assessment of quality of life is important when planning very complex regimens.

Resistance

It was originally noted that the duration of ZDV therapy correlates with the presence of resistance mutations (64). Resistance mutations were studied in PACTG 377, and virological failure was associated with the early acquisition of NVP and 3TC resistance mutations. PI resistance mutations – NFV or RTV – developed later in children remaining on the same failing regimens (65).

It is possible that the selection of resistance mutations may impair viral fitness (66). However in the PENTA 5 trial the sequential development of resistance mutations to 3TC, NFV, AZT, and ABC was noted with increasing time since virological failure (55). The PERA trial (a randomised controlled trial on the use of resistance assays) will provide data on the role of resistance assays in clinical practice, and paediatricians are encouraged to enter children into this trial. European guidelines for the use of resistance assays have recently been published (67).

Toxicity

Many children have now been on HAART for 5 years, and only the principal drug related toxicities are discussed below.

Lipodystrophy

In the first major paediatric survey on lipodystrophy (LD), Babl reported a 1 % prevalence in PACTG centres in 1999 (68). However, subsequent small studies are hampered by the lack of a standard definition of lipodystrophy in the growing child. A cross sectional study of 39 children (80% on PI) demonstrated lipodystrophy in 13, of whom 8 had truncal, 3 peripheral, and 2 combined lipodystrophy (both severe, and both adolescents). Evidence of dyslipaemia was seen in around 20% of children, but this was not significantly associated with lipodystrophy (8). Arpadi studied 28 children, and found 8 children had mild fat redistribution on DEXA scan. Children with LD had significantly lower CD4% at baseline, and higher triglycerides on follow up

(69). In other smaller studies LD has been reported in around a third of children on HAART for over 2 years, with no clear association with specific drugs, although peripheral lipoatrophy may be associated with stavudine use (70,71). Hyperlipidaemia is being increasingly reported, but currently most clinicians are not changing ART therapy or treating with cholesterol lowering drugs. There are increasing number of reports of bone demineralisation, glucose intolerance, and lactic acidemia in children (72).

Hypersensitivity

There has been increasing recognition of hypersensitivity related to nevirapine and (less commonly) efavirenz. Although a rash is common, severe hepatitis can also rarely occur. Hypersensitivity reactions have also been reported with abacavir causing fever, fatigue, GI and respiratory symptoms, with and without a rash. This occurs in 2-3% of children commencing abacavir, usually within the first month. If this is suspected, a specialist should stop the drug, and the child must not be rechallenged.

New Drugs

Both new classes of ART, and new drugs in the current classes, which may be active in children with resistance mutations, are in late stages of development. The fusion inhibitor T-20 was well tolerated in phase I study, which showed 6 out of 8 children achieving a >1 log reduction in VL by week 8, but needs to be given by subcutaneous injection (73). There are very limited data yet on other important drugs under study, including the nucleotide analogue - tenofovir, a new NRTI - emtricitabine, the PI - atazanavir, and the non - peptidic PI - tipranavir.

Conclusion

There is an urgent need for randomised studies on different ART regimens in children, particularly comparing starting with PI, or NNRTI, based combinations, and when to switch therapy following virological failure. Both these questions are being addressed in the Penpact 1 trial. Further research is needed on the use of triple NRTI regimens in children. Better tools to assess and manage problems with adherence are required. The roles of immunotherapy (IL-2), therapeutic drug monitoring (TDM), structure treatment interruptions (STI), and ART regimen simplification, all await further data from clinical trials. These guidelines will be updated every two years, and are on the PENTA website www.pentatrials.org.

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Table 1.

Approximate 5-year mortality rates in children with HIV infection not on antiretroviral therapy [adapted from Mofenson et al (33) and Palumbo et al (30)].

Mortality (5 Years)	Viral load and CD4%
<10%	VL <50,000 and CD4% >25%
10 - 20%	VL <100,000 and CD4% >15%
30 - 40 %	VL >100,000 and CD4% >15%
70 - 80 %	VL >100,000 and CD4% <15%

Table 2

Recommendation on when to start ART

Infants	Children over 12 months of age:
1) Always start if any of the below: <ul style="list-style-type: none"> • clinical stage C • CD4 < 20% • rapidly falling CD4% (irrespective of value) and/or a VL persistently > 10⁶ copies/ml 2) Consider ART in any infant irrespective of clinical or immunological stage	1). Always start ART if: Clinical stage C or CD4 <15% 2). Consider ART if : Clinical stage B* or CD 4 <20% or VL >5 log *Some Authors recommend starting if clinical stage B, but there was no consensus 3). Defer ART if Stage N or A disease, and CD4 > 20 %, and, Low VL <5 log

Table 3

Summary of recommendations of which ART to use to commence therapy

A). First Choice	B). Second Choice
<i>Either</i> 2 NRTI ¹ + 1 PI ² <i>Or</i> 2 NRTI + 1 NNRTI ³	2 NRTI + ABC ¹ NRTI combinations: ZDV+ddI; ZDV+3TC; ddI+d4T, d4T+3TC, ZDV+ABC, 3TC+ABC ² PI: NFV or RTV or Lopinavir/r ³ NNRTI: NVP or EFV (if age >4years)

Table 4 – Summary of drug dosages and toxicity.

NAME OF DRUG	TOTAL DAILY DOSE (FREQUENCY)	MAJOR TOXICITIES	OTHER COMMENTS
<i>NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS</i>			
Zidovudine (ZDV, AZT, Retrovir)	Oral 360 mg/m ² /day (divide BD) Neonatal dose 2mg/kg q 6 hourly IV 120 mg/m ² 6 hourly or 20 mg/m ² /hour	Neutropenia; anaemia; nausea; headaches; myopathy (rare)	Large volume of syrup not well tolerated in older children. Double dose for HIV encephalopathy
Didanosine (ddI, dideoxyinosine, Videx)	240 mg/m ² /day (OD or divide BD) (>60kg 200mg BD or 400mg OD) Enteric Coated 125/200/250/400 mg capsules OD for older children	Pancreatitis rare (dose related); peripheral neuropathy rare (dose related); diarrhoea and abdominal pain.	Constituted suspension stable for 30 days in fridge. Ideally taken 1 hour before food or two hours after, but may be less important in children.
Zalcitabine (ddC, dideoxycytidine, Hivid)	0.03mg/kg/day (divide BD)	headache, GI upset, Peripheral neuropathy; pancreatitis rare in children; hepatic toxicity; oral ulcers	Small tablets – syrup no longer available.
Stavudine (d4T, Zerit)	2mg/kg/day (up to 30kg) (divide BD) 30-60 kg – 30 mg BD > 60 kg 40 mg BD	headache, GI upset, rash, Peripheral neuropathy and pancreatitis (rare)	Large volume of suspension; capsules opened up well tolerated. Keep solution refrigerated. Stable for 30 days. Can give with food.
Lamivudine (3TC, Epivir)	8mg/kg/day (divide BD) In neonates < 30 days 4mg/kg/day given 12 hourly :>60kg 150mg (BD) Combivir ZDV 300mg +3TC 150mg	headache, abdo pain, pancreatitis, peripheral neuropathy, and neutropenia, abnormal LFT's - all rare	Well tolerated Store solution at room temperature (use within one month of opening)
Abacavir (ABC, GW 1592U89, Ziagen)	16mg/kg/day (divide BD) Adult 300 mg BD. Trizivir – ZDV 300mg+3TC 150 mg + ABC 300mg	1-3% may develop hypersensitivity reaction, fever, malaise, mucositis +/- rashes, usually in first 6 weeks STOP DRUG - DO NOT RECHALLENGE.	Syrup well tolerated or crush tablets. MUST WARN PARENTS ABOUT HYPERSENSITIVITY REACTION.

Table 4 – Summary of drug dosages and toxicity. - continued

NAME OF DRUG	TOTAL DAILY DOSE (FREQUENCY)	MAJOR TOXICITIES	OTHER COMMENTS
<i>NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS</i>			
Nevirapine (NVP, Viramune)	3-400 mg/m ² /day (divide BD). Start at 150-200 mg/m ² /day once daily for 2 weeks then increase to 3-400 mg/m ² /day if no rash. Maximum 400 mg OD.	Rash 10-20% can treat through, Stevens-Johnson very rare, but STOP drug. Monitor liver enzymes. Induces cytochrome P450. Drug interactions Decreases concentrations of most PI	Can be given with food Few data on use with PI. Practice is to increase PI dose by about 30%.
Efavirenz (EFV, Sustiva)	Limited PK in <3 years. 15mg/kg or 10-15kg- 200 mg; 15-20 kg- 250 mg; 20-25 kg - 300 mg; 25-33kg - 350 mg; 33 - 40 kg 400 mg; > 40 kg - 600mg. OD. Syrup increase dose.	Rash (mild). CNS toxicity, somnolence, abnormal dreams, "Spacey kids". Drug interactions.	Syrup available. Best given as bedtime dosing to reduce CNS side effects.
Delavirdine (DLV, Rescriptor)	Paediatric dose under study. Adult dose 600 mg BD.	headache, fatigue, rash. Drug interactions.	Dispersible tablets can be dissolved in water/Coke. Rarely used.
<i>PROTEASE INHIBITORS</i>			
Indinavir (IDV, Crixivan)	Do not use in neonates. 1500mg/m ² /day (divide TDS) Adult 800 mg every 8 hours.	Nausea; hyperbilirubinaemia (10%) Renal stones/nephritis (4%); haemolytic anaemia, liver dysfunction rare. Abnormal lipids	Do not take with meals. Complex formula for syrup available. Advise fluid intake +++ Not Coke. Drug interactions.
Ritonavir (RTV, Norvir)	800mg/m ² /day (divide BD) Start with 250mg/m ² /dose 12 hourly & increase over 5 days. Infants 900 mg/m ² /day. (Syrup 80 mg/ml)	GI intolerance ++, headache; increase liver enzymes; abnormal lipids.	Take with food but liquid tastes bitter. Can help to take with peanut butter and follow with chocolate sauce or cheese. Note drug interactions.
Saquinavir (SQV, Fortovase)	150 mg/kg/day (divide TDS)	Rash; headache; GI upset; Abnormal lipids	Give with food. Sun photosensitivity. Drug interactions
Nelfinavir (NFV, Viracept)	110-120mg/kg/day (divide BD) Adolescents need > than adult doses Crush tablets; Powder available Infants 150 mg/kg/day	Mild /moderate diarrhoea Vomiting; rash; Abnormal lipids	Take with food. Drug interactions.
Lopinavir/ritonavir, (LPV/r, Kaletra)	450/112.5 – 600/150 mg/m ² /day (divide BD). Higher dose used with NNRTI. (syrup 80/20 mg/ml)	Rash (2%), GI intolerance, abnormal lipids.	Liquid formulation – low volume bitter taste. Capsules large. Take with food. Drug interactions.
Amprenavir (APV, Agenerase)	40mg/kg/day (divide BD) capsules Increase dose for syrup	GI upset. Abnormal lipids	Large volume of syrup – bitter taste. 150 mg capsules are very large; alternatively many small capsules (50mg) have to be taken.