

PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection

PENTA Steering Committee

PENTA Guidelines aim to provide practical recommendations for treating children with HIV infection in Europe. Changes to guidance since 2004 have been informed by new evidence and by expectations of better outcomes following the ongoing success of antiretroviral therapy (ART). Participation in PENTA trials of simplifying treatment is encouraged. The main changes are in the following sections:

'When to start ART': Treatment is recommended for all infants, and at higher CD4 cell counts and percentages in older children, in line with changes to adult guidelines. The number of age bands has been reduced to simplify and harmonize with other paediatric guidelines. Greater emphasis is placed on CD4 cell count in children over 5 years, and guidance is provided where CD4% and CD4 criteria differ.

'What to start with': A three-drug regimen of two nucleoside reverse transcriptase inhibitors (NRTIs) with either a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a boosted protease inhibitor (PI) remains the first choice combination. Lamivudine and abacavir are the NRTI backbone of choice for most children, based on long-term follow-up in the PENTA 5 trial. Stavudine is no longer recommended. Whether to start with an NNRTI or PI remains unclear, but PENPACT 1 trial results in 2009 may help to inform this. All PIs should be ritonavir boosted.

Recommendations on use of resistance testing, therapeutic drug monitoring and HLA testing draw from data in adults and from European paediatric cohort studies.

Recently updated US and WHO paediatric guidelines provide more detailed review of the evidence base. Differences between guidelines are highlighted and explained.

Keywords: antiretroviral therapy, child, HIV-1

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1. Summary of recommendations

These updated PENTA Guidelines [1] aim to provide a practical summary of recommendations for treating children with HIV-1 infection in Europe. Recently updated adult [2] and WHO [3] guidelines provide a more detailed review of the evidence base. Differences from other paediatric guidelines are highlighted and explained. Management of HIV-2 is not addressed here, and HIV is considered to refer to HIV-1 throughout this document.

1.1. Aims of paediatric antiretroviral therapy

The aims of treatment with antiretroviral (ARV) drugs in HIV-infected children are to achieve and sustain full HIV RNA viral load (VL) suppression and minimize short- and long-term ARV drug toxicity. Sustained VL suppression should prevent the evolution of viral drug resistance and

allow normal immune function, which in turn should prevent opportunistic infections (OIs), HIV encephalopathy, malignancy and progression of HIV disease, and allow normal growth and development.

Achieving these goals requires that children with HIV have access to multidisciplinary care teams, and supervision of medical care by clinicians experienced in the management of paediatric HIV, either directly or through treatment networks.

1.2. Diagnosis of HIV

For HIV in children aged <18 months, HIV infection should be diagnosed by a positive RNA or DNA polymerase chain reaction (PCR), and by positive serology in older children. A repeat test should always be performed to confirm the diagnosis.

1.3. Pre-treatment monitoring and baseline investigations

A detailed history of any possible previous antiretroviral therapy (ART) given to the child and mother (or other likely source of infection) should be documented.

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Children should be examined clinically for OIs and complications of HIV, including assessment of growth and development. Baseline pre-ART investigations should include HIV RNA VL, T-cell subsets including CD4 cell count and percentage (CD4), testing for other blood-borne infections (especially hepatitis B and C), haematology and biochemistry profile, as well as HIV resistance genotype and HLA B*5701 genotype prior to abacavir (ABC) therapy. Clinical monitoring and measurement of CD4 and VL should be repeated at least every 3–4 months in well children who do not need to start ART, and more frequently in infants and in older children approaching treatment thresholds.

1.4. Prophylaxis against OIs

All HIV-infected infants aged over 1 month should receive prophylaxis against *Pneumocystis jiroveci* pneumonia (formerly *Pneumocystis carinii* pneumonia). Children aged 1–4 years should receive prophylaxis against *Pneumocystis* if they have a CD4 count below 500 cells/ μ L or 20% of total lymphocyte count. Children aged 5 and above should receive such prophylaxis if they have a CD4 count below 200–250 cells/ μ L or < 15%.

There are few data to inform recommendations for routine primary prophylaxis against other OIs. Children should be fully immunised (except BCG).

1.5. When to start ART

ART should be started urgently in all infants irrespective of clinical or immunological stage. In particular, in babies infected despite attempted prevention of mother-to-child transmission (pMTCT), ART should be commenced as soon as the diagnosis of infection is confirmed.

ART should be started in all children aged 12 months or more with symptomatic disease (CDC clinical stage B or C or WHO stage 3 or 4). Some children with milder symptoms of CDC stage B may not need to start treatment urgently.

In children aged more than 12 months with no or minor symptoms (CDC clinical stage A or N or WHO stage 1 or 2), ART should be started when the CD4 count or percentage falls below age-specific thresholds:

1 to <3 years	CD4 <25%, or <1000 cells/ μ L
3 to <5 years	CD4 <20%, or <500 cells/ μ L
Above 5 years	CD4 count <350 cells/ μ L

In children aged more than 12 months and with no or minor symptoms, and CD4 cell counts and percentages above the age-appropriate threshold, ART should be considered if the VL exceeds 100 000 copies/mL.

Some clinicians may prefer to calculate risks of progression to AIDS or death for individual children using the HPPMCS risk calculator (www.hppmcs.org/) and make individualized treatment decisions based on these risks.

These treatment thresholds differ significantly from recommendations in the 2004 guidelines. Reasons for these changes include: (1) new evidence of the clinical efficacy of early ART in infants; (2) new data from adult cohorts and the SMART trial which have resulted in raising the CD4 threshold for ART initiation in adults in well-resourced countries; (3) data suggesting that CD4 cell count rather than percentage is the more appropriate predictor in children from age 5 years; and (4) availability of new ARV drugs including two new classes.

Issues likely to affect adherence should always be considered and addressed before starting therapy.

1.6. What to start with

The choice of drugs depends on available formulations suitable for the individual child, taking into consideration age, developmental level and carer circumstances.

The current preferred first-line ART regimen for previously untreated children with no evidence of ARV resistance comprises two nucleoside reverse transcriptase inhibitors (NRTIs) with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir (RTV)-boosted protease inhibitor (PI). A PI may be preferred to an NNRTI in children with anticipated poor adherence.

The preferred NRTI combinations are ABC and lamivudine (3TC) for children who are HLA-B *5701 negative, and zidovudine (ZDV) and 3TC for children who are HLA-B *5701 positive. Both of these are available as combination tablets for older children. A third combination tablet of tenofovir and emtricitabine (FTC) is increasingly popular for use in adult patients, and may be useful in adolescents. Tenofovir is not yet licensed for use in children aged < 18 years, and data on safe long-term use from a young age are lacking.

The preferred NNRTI is nevirapine (NVP) for children aged < 3 years, and efavirenz (EFV) for older children. The preferred PI is ritonavir-boosted lopinavir (*Kaletra*) for young children. Alternative boosted PIs may be considered for older children, including fosamprenavir/r and darunavir/r, which are licensed from age 6 years, atazanavir/r, which is licensed from age 6 years in the United States, but not yet in Europe, and saquinavir/r, which is not licensed in children, but may be suitable for adolescents.

1.7. Monitoring on ART

Clinical and laboratory monitoring should take place more frequently after initiating or changing therapy, and this

needs to continue in infants who are growing rapidly and in children with adherence difficulties. Once children are established on treatment, clinical and laboratory monitoring should be undertaken every 3–4 months in the same way as before starting treatment, with the important additions of monitoring adherence and for drug toxicities and interactions.

There are no studies to inform recommendations for routine use of therapeutic drug monitoring (TDM) in children. However, it may be useful in circumstances where drug doses are less well established or there is suspected toxicity, failure or likely drug interactions.

1.8. Adherence

Assessing, maintaining and supporting adherence to the ART regimen is perhaps the single most important component of treatment. Informing and educating children of their HIV diagnosis in gradual, age-appropriate steps is essential in enabling them to optimize their adherence.

1.9. Drug toxicities and interactions

Toxicities depend on the individual drugs and ART combination, and should be monitored at each clinic visit.

1.10. Treatment interruptions

Planned treatment interruptions in children are not currently recommended. Treatment is often discontinued for other reasons, and this requires particular care when the regimen contains an NNRTI, with a low barrier to resistance, and usually a much longer half-life than NRTIs in the regimen. Specific strategies to stop these drugs safely are recommended.

1.11. When to switch ARV drugs for treatment failure

There are no data on when to switch ART in children with detectable viraemia in order to minimize the evolution of drug-resistant virus. Available drug regimens, viral resistance profiles, adherence issues and readiness of the family and child to switch all need to be considered. Results of PENPACT 1 in late 2009 should help to resolve this issue.

1.12. What to switch to

Choice of second-line and subsequent ART regimens should be informed by previous drug history and adherence, resistance testing, expert advice and suitable formulations available for the individual child.

1.13. Coinfection

Specific coinfections with tuberculosis (TB) or hepatitis may affect the timing and composition of ART.

1.14. Clinical trials

Many important recommendations are not yet based on randomized controlled trial (RCT) evidence, and children should be entered into high-quality trials where this is possible.

1.15. Specific drugs

Information on specific drugs, including newly available drugs and drug classes is summarized in Table S1 of the online version (www.pentatrials.org/guidelines.htm). Additional information is available from US guidelines [4].

2. Introduction

- These guidelines apply to children with HIV infection in Europe.
- All HIV-infected infants should start ART as a matter of urgency.
- Thresholds for starting ART in asymptomatic children have changed significantly in the light of new evidence.
- New drugs are available, but not yet recommended for first- or second-line treatment in children.

These 2009 PENTA guidelines have been updated from those of 2004 [1], and make recommendations based on updated evidence and new developments. They also draw on new evidence from the adult HIV literature and guidelines [2]. The aim is to provide a practical guide to treatment rather than comprehensive details of all the evidence on ART in children. More detailed information for resource-rich and resource-poor settings is available from recently updated US and WHO paediatric guidelines [3,4].

These guidelines seek to optimize treatment for children in Europe. However, particularly during adolescence, care may need to be individualized. Therefore, this document should not be seen as a standard for litigation.

Since 2004, the main developments in paediatric HIV have been the availability of ARTs in less developed countries, new drugs, the ongoing success of ART in developed countries, and some new data to better inform treatment strategies.

The availability of ARV drugs in less developed countries is a major development, but is not the subject of this document. This guideline specifically focuses on children in Europe, but will have relevance for children in middle-income countries and settings. Special considera-

Table 1a Comparison of current PENTA, WHO and US treatment thresholds

	PENTA 2009	US 2008	WHO 2008
0–11 months			
Clinical	Treat all	Treat all	Treat all
Immunological			
Virological			
12–35 months			
Clinical	Treat CDC Stage B or C/WHO stage 3 or 4	Treat CDC Stage B or C	Treat WHO Stage 4 and severe 3
Immunological [CD4%/count]	Treat <25% or <1000 cells/ μ L	Treat <25%	Treat <20% or <750 cells/ μ L
Virological	Consider >100 000 copies/mL	Consider >100 000 copies/mL	
36–59 months			
Clinical	Treat CDC Stage B or C/WHO stage 3 or 4	Treat CDC Stage B or C	Treat WHO Stage 4 and severe 3
Immunological [CD4%/count]	Treat <20% or <500 cells/ μ L	Treat <25%	Treat <20% or <350 cells/ μ L
Virological	Consider >100 000 copies/mL	Consider >100 000 copies/mL	
5 years +			
Clinical	Treat CDC Stage B or C/WHO stage 3 or 4	Treat CDC Stage B or C	Treat WHO Stage 4 and severe 3
Immunological [CD4%/count]	Treat <350 cells/ μ L	Treat <350 cells/ μ L	Treat <15% or <200 cells/ μ L
Virological	Consider >100 000 copies/mL	Consider >100 000 copies/mL	

Table 1b Comparison of PENTA 2009 and 2004 guidelines

		PENTA 2009		PENTA 2004
Clinical	0–11 months	Treat all	0–11 months	Treat CDC Stage B or C
Immunological				Treat <35%
Virological				Consider >1 000 000 copies/mL
Clinical	12–35 months	Treat CDC Stage B or C/WHO stage 3 or 4	12–47 months	Treat CDC Stage C
Immunological [CD4%/count]		Treat <25% or <1000 cells/ μ L		Treat <20%
Virological		Consider >100 000 copies/mL		Consider >250 000 copies/mL
Clinical	36–59 months	Treat CDC Stage B or C/WHO stage 3 or 4	4–12 years	Treat CDC Stage C
Immunological [CD4%/count]		Treat <20% or <500 cells/ μ L		Treat <15%
Virological		Consider >100 000 copies/mL		Consider >250 000 copies/mL
Clinical	5 years +	Treat CDC Stage B or C/WHO stage 3 or 4	13–17 years	Treat CDC Stage C
Immunological [CD4%/count]		Treat <350 cells/ μ L		Treat <200 cells/ μ L
Virological		Consider >100 000 copies/mL		Consider 200–350 cells/ μ L
				Consider >250 000 copies/mL

tions for children in resource-limited settings where background rates of concomitant infections and malnutrition are much higher are not considered here, and the reader is referred to WHO guidelines [3]. Differences from WHO and US guidelines will be referred to where relevant in the document and are summarized in Table 1.

New drugs and two new classes of ARTs (integrase inhibitors and CCR5 inhibitors) have recently become available for adults. Data are available on the paediatric use of several RTV-boosted PIs. Some are licensed for use in older children, and more may soon follow. However, drugs from the two new classes are not yet licensed for use in children, although Phase I/II studies are in progress. Even in adults, drugs from new classes have not been used long enough to determine their best place alongside older

drugs in the optimal sequence of first-line and subsequent ART combinations. We also know less about long-term toxicities of newer drugs, which are particularly important for children who may remain on ART for decades.

There remains a paucity of data from RCTs on which to base ART guidelines in children; available trials also tend to be small. Therefore, we continue to rely on cohort studies, extrapolation from adult data and expert opinion. Wherever possible, children should be entered into clinical trials, some of which may challenge current guidance.

Increasing survival of children with HIV gives rise to increasingly complex care needs. It is essential that children are looked after by multidisciplinary teams. There also needs to be access to expert medical advice on treatment, either by direct supervision of treatment, or through clinical networks.

Changes to this guidance since 2004 have been informed by new evidence and by expectations of better outcomes because of the ongoing success of ART in children. The main changes from the 2004 guideline recommendations are in the following sections:

- (1) *'When to start ART'*: Treatment initiation is recommended for all infants, and at higher CD4 cell counts and percentages in older children. The number of age bands has been reduced to simplify guidance and to harmonize with other guidelines. Greater emphasis is placed on CD4 cell count in children from age 5 years, and some guidance is provided where CD4% and CD4 cell count thresholds are discordant.
- (2) *'What to start with'*: 3TC and ABC are recommended as the NRTI backbone of choice for most children, based on long-term follow-up in the PENTA 5 trial. Stavudine (d4T) is no longer recommended. Whether to start with an NNRTI or PI remains unclear, but PENPACT 1 trial results may help to inform this question. PI-based regimens should be RTV boosted.
- (3) *Recommendations on use of resistance testing, TDM and HLA testing* draw from data in adults as well as more recent data from paediatric cohort studies in Europe.
- (4) *ARV drug information sheets* are provided online which include data on licensed doses, and refer to new data on doses and simplification of drug regimens. They also indicate where data differ from other guidelines. Readers may wish to consult WHO guidelines [3] for use of body-surface-area-derived simplified weight band tables, particularly for use of fixed-dose combinations (FDCs) in children.

3. Diagnosis, baseline investigations and pre-treatment monitoring

- HIV diagnosis requires repeat positive PCR in infants and serology in older children.
- A detailed history of any possible previous ART given to the child and /or mother (or other likely source of infection) should be documented.
- Drug history, viral resistance profile and HLA B*5701 type should be documented at baseline.
- Clinical assessment, CD4 cell count and viral load should be carried out 3–4 monthly in children who are stable off ART.
- Infants and older children who may need ART soon should be assessed more frequently.

Optimal treatment of HIV in children depends upon timely diagnosis. This requires early HIV diagnosis of all infants born to HIV-infected women and prompt testing of infants

or older children at increased risk or with symptoms and signs of HIV infection. Infants of women with HIV infection will all be antibody positive because of transplacental transfer of maternal antibodies, and require a PCR test to confirm or exclude the diagnosis. Either RNA or DNA PCR may be used, depending on local availability. At least two positive PCRs on separate samples from the baby (not umbilical cord) are required to confirm a diagnosis, and at least two separate negative PCRs after stopping post-exposure prophylaxis are required to confirm that an exposed baby is uninfected. Expert advice should be sought before starting therapy or discharging a baby from follow-up if there is any doubt about the interpretation of the results. It should be remembered that babies of infected women may become infected after initial negative tests if they are breastfed [3–7].

Infants and children who present with symptoms consistent with HIV infection should initially have an HIV antibody test. If positive, this will require a confirmatory PCR in children aged <18 months, and a confirmatory repeat antibody test in older children. Paediatricians (and adult physicians) need to be aware of the increasing proportion of newly diagnosed HIV-infected children and adolescents in Europe coming from other higher prevalence countries [8]. HIV testing should be considered early in any newly arrived child or young person presenting to health services. All children born to HIV-infected mothers should be tested for HIV whatever their age as infected children may remain asymptomatic throughout childhood.

Once a diagnosis of HIV is confirmed, children should be assessed clinically, including growth and development, to allow staging of HIV according to CDC and/or WHO classifications [3,4,9,10], which are broadly similar. Both classifications are referred to in this guideline.

To plan future ART, it is important to know and document whether the child has been exposed to previous ART, either *in utero*, as post-exposure prophylaxis or as therapy (e.g. in the country of origin). If available, the ART history of the mother or other source case should also be documented. HIV genotypic resistance testing is recommended at baseline, whether or not there is a history of previous ART exposure. If available, the results of resistance testing on the source case, as close as possible to the time of transmission, should also be documented. Other investigations after HIV diagnosis should include HIV RNA VL, CD4 percentage and cell count, tests for other vertically transmitted infections (Hepatitis B and C, toxoplasma, CMV, syphilis), full blood count (FBC), biochemistry profile, and, where available, HLA B*5701. This last test may be done in all patients at baseline to plan future therapy, but it should certainly be done before starting treatment with ABC [11].

A full vaccine history should be taken and if necessary serology performed to confirm immunity (see baseline investigations at www.chiva.org.uk). A baseline chest radiograph allows assessment for respiratory complications, including lymphoid interstitial pneumonitis and TB. Infants and children with advanced HIV disease should have an ophthalmic examination for evidence of retinitis, as well as baseline blood PCR for cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Children from TB-endemic areas should have a baseline assessment for TB, including CXR and immune response test (Mantoux test or interferon gamma release assay).

For children not yet requiring ART, visits to assess clinical status and perform laboratory monitoring should be at intervals of no longer than 3–4 months. Children approaching thresholds for starting treatment, and all infants, should be seen more frequently. Routine clinic monitoring should include clinical examination and neurodevelopmental assessment, measurement of growth, nutritional and pubertal status, and measurement of CD4 values, VL, FBC, serum electrolytes, renal and liver function, and less frequent (annual) measurement of lipids.

Regular assessment should be made of the child and carers' knowledge and understanding of HIV, of adherence to any other medication, and of factors likely to affect adherence to ART when it is started.

The medical care of children with HIV infection has changed and is more successful, but remains complex. It is important for children to have access to care by experts with experience of managing children with HIV infection. This may be by direct supervision of care, or through clinical care networks. The complex social and psychological needs of children surviving into adolescence and adulthood require input from many professionals, and care by a multidisciplinary team is essential.

4. Prophylaxis against OIs

- Prophylaxis against *Pneumocystis* pneumonia should be given to all infants from age one month and to older children with low CD4 cell counts. Cotrimoxazole is the drug of first choice.
- No routine primary prophylaxis against other infections is recommended.
- Immunisation status should be checked, and boosted if required.

Prophylaxis with cotrimoxazole is highly effective at preventing potentially life-threatening infection with *P. jiroveci* pneumonia (formerly *P. carinii* pneumonia), and

also at reducing bacterial infections [12,13]. As a result of their greater susceptibility to severe *Pneumocystis* infection, all HIV-infected infants should receive prophylaxis from age 1 month until their first birthday [14]. Cotrimoxazole is the first choice drug unless contra-indicated.

Children aged 1–4 years should receive prophylaxis against *Pneumocystis* if they have a CD4 count below 500 cells/ μ L or 20% of total lymphocyte count. Children aged 5 and above should receive prophylaxis against *Pneumocystis* if they have a CD4 count below 200–250 cells/ μ L or < 15%. Prophylaxis may also be considered for children travelling back to countries with high prevalence of bacterial infections, irrespective of their CD4 cell count/percentage and current treatment status [13]. Once ART has been started and the CD4 cell count has risen, risks of *Pneumocystis* decrease [15,16]. Most paediatricians stop cotrimoxazole in children living in well-resourced settings after 6 months with a normal CD4 cell count.

Prophylaxis against other infections, including CMV, atypical *Mycobacteria* and fungal infections other than *Pneumocystis*, has been suggested for those with very low CD4 cell counts. There is insufficient evidence to make any recommendations for routine primary prophylaxis, but specific guidance is available from national websites [17]. Immunoglobulin infusions were used to reduce the rates of OIs before the advent of ART. They remain an option, but are not now routinely recommended. Prophylaxis against TB can be considered for children visiting countries highly endemic for TB, and also in all HIV-infected children exposed to active TB.

A full vaccination history should be obtained, and, if appropriate, vaccine responses may be confirmed by serological testing. Children should be fully immunized according to national or forthcoming PENTA immunization guidelines. They should not receive Bacillus Calmette-Guérin (BCG), and yellow fever and live oral typhoid vaccines for travel are contraindicated with low CD4 cell counts.

5. When to start ART

- ART should be started in all infants even if asymptomatic.
- ART should be started in all children with significant disease (CDC stage B or C WHO stage 3 or 4).
- ART should be started in asymptomatic older children based on age-specific CD4 cell counts.
- ART initiation in older children is recommended at higher CD4 cell counts than in the 2004 PENTA

guidelines. This reflects new evidence and is in line with the US and WHO guidelines.

5.1. Infants

5.1.1. Asymptomatic infants

PENTA guidelines 2004 [1] recommended immediate treatment for infants with clinical symptoms or CD4% < 35%, and noted that some experts would also start ART early in asymptomatic infants; deferred treatment with close clinical and laboratory monitoring remained an option.

There is now new evidence to recommend starting ART as early as possible in all HIV-infected infants (under 1 year of age), irrespective of clinical or immunological status. This guidance is the same in US and WHO guidelines [3,4]. The evidence comes from an interim analysis of the South African randomized controlled Children with HIV Early antiRetroviral therapy (CHER) trial [18] which showed a fourfold reduction in mortality among infants starting ART before 3 months of age compared with those starting according to WHO guidelines (CD4% 25% or WHO stage 3 or 4). In addition, a fourfold reduction in HIV progression/mortality was observed among infants starting ART at < 3 months of age compared with later in a large individual infant cohort meta-analysis [European Infant Collaboration (EIC)] [19], thus confirming that results in South Africa can be extrapolated to Europe. The reader is also referred to US [4] and WHO [3] guidelines for more details.

Universal treatment of all infants with HIV is a challenge. In particular, the risks of developing drug-resistant virus are significant in the face of high VLs, especially when treatment is unsuccessful or adherence is partial; problems of resistance and toxicity may only become manifest in the longer term. However, these problems are dwarfed by such marked improvements in short-term mortality and disease progression (in particular prevention of irreversible HIV encephalopathy). It should be noted that both the CHER and EIC results apply most directly to babies infected despite attempted prevention of pMTCT, who may have faster rates of disease progression. It is less clear-cut whether this evidence can be applied to asymptomatic infants diagnosed after the age of 6 months who generally have not been exposed to pMTCT. However, consensus in this guideline, in line with US and WHO guidelines [3,4], is that all infants with HIV should be started on ART as soon as possible, irrespective of clinical status and laboratory marker results.

Despite time pressure to start ART in infants, it remains crucial to review the infant frequently when starting treatment and spend time working on adherence with the family at all visits, in order to limit the risk of virological failure and subsequent rapid evolution of resistant virus.

5.1.2. Symptomatic infants

Symptomatic infants presenting with severe illness, should start ART as soon as possible. Debate remains about whether ART should be started immediately or deferred until the presenting illness has been treated. There is no evidence to inform this, and it is recommended that ART be started as soon as the child is stable.

5.2. Children over 12 months of age

Starting ART is recommended in all children with significant symptoms, and in asymptomatic children with CD4 cell counts or percentages below recommended age-related thresholds. Starting ART should also be considered in those with a high HIV RNA VL as they are more likely to progress rapidly to symptoms or rapid fall of CD4 values. The evidence for these recommendations is based predominantly on analysis of paediatric and adult cohort data and extrapolation from the adult SMART trial [20–25]. There are no data from randomized trials on when to start ART in older children.

Children with AIDS or significant symptoms (CDC Clinical Category C or B or WHO stage 3 or 4) have a higher mortality risk [26] and should start ART as a matter of urgency. 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. CDC clinical category B covers a wide range of disease severity, and it is recognized that some children with milder stage B disease may have treatment deferred if their CD4 cell count allows this.

The 2004 PENTA guidelines [1] mainly used analysis of pre-highly active antiretroviral therapy (HAART) cohort data in the HPPMCS study [22] to recommend CD4 (and VL) thresholds for initiating ART in three age bands in asymptomatic children after infancy (1–3; 4–8; > 8 years). These thresholds were determined by arbitrary age-related disease progression risks in the next 12 months which were deemed unacceptable, namely a 10% risk of AIDS or 5% risk of death. These risks would now be deemed acceptably high.

In these updated 2009 guidelines, we take account of continued success of ART in children [8,27] and new data suggesting ART should start earlier in adults. We also re-examined the HPPMCS, age-related CD4 thresholds. Progression risk remains highly variable, particularly for the youngest children, and is based on historical cohort data. It is recognized that the new recommended thresholds are still based on expert opinion and remain arbitrary. The age bands (1–<3; 3–<5; ≥ 5 years) differ from the 2004 guideline, in order to provide harmony with other guidelines (which also largely use HPPMCS data) [3,4]. Of note, an individual child's risk levels can be derived from the

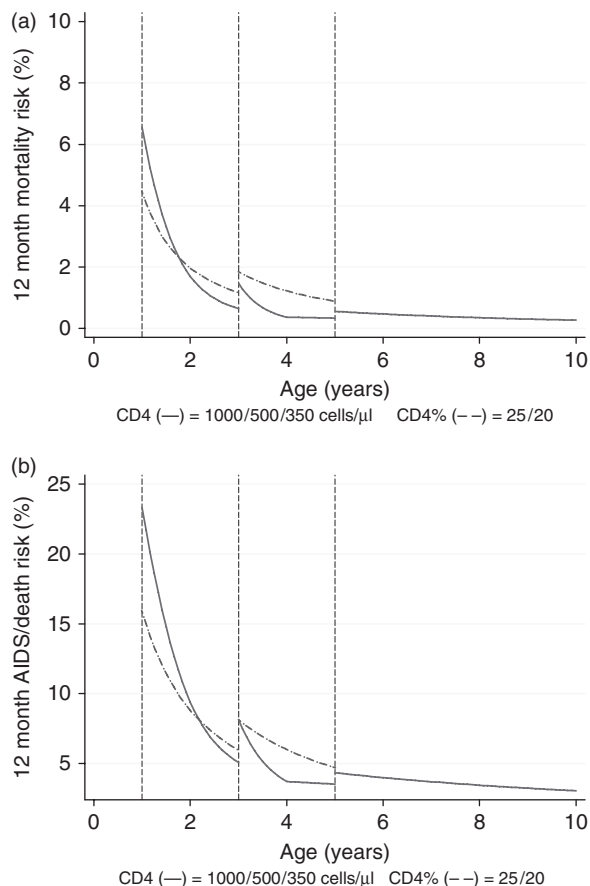


Fig. 1 12-month risk of disease progression (a) death (b) AIDS or death, at selected thresholds for CD4 cell count and CD4 percent. Solid line (CD4 count, cells/ μ L): 1000 (1–3 years), 500 (3–5 years), 350 (5–10 years). Dashed line (CD4 percent): 25% (1–3 years), 20% (3–5 years). Source: HPPMCS [22–24].

HPPMCS data using an on-line calculator available at www.hppmcs.org/. The treatment thresholds in this guideline keep the risk of mortality below 2% and the AIDS progression risk below 5% in older children, but progression risk is higher and more variable in the first few years after infancy.

Figure 1 shows details of the risks of progression to AIDS or death for different age strata at the treatment initiation thresholds in these guidelines.

The evidence for changing age-related CD4 thresholds, based on HPPMCS data are as follows:

(1) Analysis of adult data: Data from the SMART trial clearly showed that adults with CD4 counts between 250 and 350 cells/ μ L have significantly better outcomes on ART than off ART [21]. This remains true in a sub-analysis of patients who had not received previous ART, confirming the benefit of starting treatment at these thresholds [25]. Adult (US and European) guidelines have changed

to recommend ART initiation at CD4 cell counts below 350 cells/ μ L [2]. This is supported by data from the UK CHIC cohort showing that in untreated adults, mortality is related to CD4 count even at values \geq 500 cells/ μ L [28].

(2) Comparison of child and adult data: Comparison of the short-term risks of disease progression in the pre-HAART adult CASCADE cohort collaboration and in children 5 years and older in the paediatric HPPMCS cohort showed that the short-term risk of disease progression was very similar in young adults (around 20 years) and children aged 5 years and older [20]. The conclusion is that absolute CD4 cell count, rather than percentage, should be used to determine treatment thresholds in children from the age of 5 years, and that children over 5 years should follow the same CD4 threshold recommendations as adults.

(3) New analyses of child data: New analyses from the HPPMCS cohorts show that CD4 cell counts are highly prognostic at ALL ages after infancy [24]. However, to obtain a uniform progression risk with the thresholds for adults and children aged 5 and over, thresholds in children aged less than 5 years would have to vary every 6 months or less. This would require too many age bands for a workable guideline, and the historical data on which progression risks are based are not robust enough to warrant ignoring the importance of practically useable guidance and the desirability of general concordance with other international guidelines. Therefore, in these updated guidelines, we propose just two age bands between 1 and 5 years. This division is the same as WHO guidance, but differs from US guidance. We also propose that CD4 cell count as well as CD4 percent thresholds be taken into account. As CD4 cell count thresholds change more with age than CD4 percent thresholds in young children, the child's age within age bands 1–3 and 3–4 years also needs to be taken into account. In the HPPMCS, 10–20% of single CD4% and CD4 cell counts would be discordant in terms of ART initiation thresholds adopted for these PENTA guidelines. However, these values were frequently concordant on a subsequent blood sample, emphasizing the importance of confirming values before making clinical decisions. If consistent discordance is observed, and particularly if the count is below the threshold although percent is not, then initiation of ART should be strongly considered.

The level of plasma HIV RNA provides some useful information in terms of risk for progression, although its prognostic significance is weaker than CD4 cell count or percent [23,29]. Consideration may be given to starting ART in asymptomatic children with HIV VL values persistently above 100 000 copies/mL even if they do not meet CD4 cell count criteria.

2009 PENTA Recommended CD4 thresholds for initiating ART

Marker	<i>Age-specific recommendation to initiate ART</i>			
	<i>< 12 months</i>	<i>1 to < 3 years</i>	<i>3 to < 5 years</i>	<i>≥ 5 years</i>
Clinical Stage	Start all	CDC B and C or WHO stage 3 and 4	CDC B and C or WHO stage 3 and 4	CDC B and C or WHO stage 3 and 4
CD4 % and CD4 count	Start all	< 25% or < 1000 cells/ μL *	< 20% or < 500 cells/ μL *	\leq 350 cells/ μL

*It is recommended that ART be started as soon as either the CD4% or the CD4 cell count threshold is consistently reached.

Rapid clinical, virological or immunological failure can occur, but in general, ART does not need to be started quickly except in infants or a child seriously ill with advanced HIV. This is especially true with these higher thresholds for initiating treatment and lower disease progression risks, particularly in older children. Time spent preparing and educating the family, particularly about adherence, is very important. Starting ART needs to be supported by the caregivers if it is to succeed. It is preferable not to start ART at the first clinic visit. Older children should know why they are taking treatment, and timing of full or partial disclosure in relation to starting ART is an important consideration. In children who have a stable CD4 cell count around a treatment threshold, it is justifiable to spend an extended time working on adherence support, disclosure or waiting for important life events to pass before starting treatment. Coinfections such as hepatitis B or C or TB may affect treatment initiation thresholds.

6. Which ART regimen to start – first line

- Children should start effective (≥ 3 drugs) ART, usually a dual NRTI backbone together with either a ritonavir-boosted PI or NNRTI.
- Children's age, HLA-B*5701 genotype, previous drug exposure, resistance profile, coinfections, available formulations and likely adherence should be taken into account when constructing a first-line regimen.
- See Table 2 for details of recommended ART regimens.

6.1. General principles of treatment

Whichever regimen is chosen, it will be useless if not taken regularly and properly. Children's doses should be checked against their age and weight or surface area at each visit, and this should be done frequently during periods of rapid growth, especially infancy. Doses should be rounded up (not

down) to convenient syrup volumes or tablet formulations, and parents should be given careful instructions on: dosage; timing; administration; repeating doses after vomiting; and seeking medical attention rather than discontinuing if drugs are refused or side effects are suspected. Supervised initiation of therapy in hospital may be appropriate for some children and families, particularly newly diagnosed infants.

The standard first-line treatment regimen remains two NRTIs with either an NNRTI or a boosted PI (see Table 2). Although baseline viral resistance remains rare in children, a pre-treatment resistance genotype should be performed, and maternal ARV drug history should be considered because resistance may be archived if the child is no longer on ART previously received.

6.2. Choice of nucleoside backbone

Factors to consider when choosing the dual NRTI combination:

- potential for resistance and cross-resistance (and hence future therapy options)
- tolerability and toxicity
- formulations including fixed-dose combinations
- dosing frequency.

d4T and ZDV cannot be used together as they are antagonistic; d4T is no longer recommended because of toxicity and should never be given with didanosine (ddl) [30]. Children arriving in Europe from resource-poor settings on FDCs containing d4T may be changed to another regimen. 3TC and FTC have similar actions and cross resistance and are interchangeable, but should not be used together.

3TC and ABC, which has superior long-term efficacy to 3TC and ZDV [31], can be given once daily to children over 3 years [32,33]. 3TC and ABC both have reasonable liquid formulations, scored and breakable tablets have recently become available, and in older children can be given as a dual FDC (Kivexa). Recent cohort-derived evidence of

Table 2 Suggested treatments [courtesy of Children's HIV Association of UK and Ireland (CHIVA)]
CHIVA Treatment Grid for Children with HIV – first- and second-line antiretroviral choices – 2009

The drug dosing in the table below is according to weight/age, but also depends on the child's ability to swallow tablets. If a child cannot swallow tablets, the regimen may need to be modified.

Prior to starting ARTs, HIV resistance and HLA B*5701 should be tested. If the virus is wild type and the patient HLA B*5701 negative, proceed with the treatment plan below. If there is baseline resistance seek advice. If the child is HLA B*5701 positive then abacavir should **not** be prescribed.

First-line antiretroviral therapy*			
< 3 years	> 3 years but < 40 kg	> 40 kg	
Nevirapine + lamivudine + abacavir (+ zidovudine [†]) [‡] or lopinavir/ritonavir + lamivudine + abacavir (+ zidovudine [†])	Efavirenz + lamivudine + abacavir [‡] or lopinavir/ritonavir + lamivudine + abacavir	Efavirenz + (emtricitabine + tenofovir [§]) or (lamivudine + abacavir [§]) [‡] or lopinavir/ritonavir [¶] + (emtricitabine + tenofovir [§]) or (lamivudine + abacavir [§])	
Most likely second-line antiretroviral therapy – when first-line NNRTI based			
< 30 kg	> 30 kg	> 40 kg	
Lopinavir/ritonavir + zidovudine + didanosine	Lopinavir/ritonavir + zidovudine + tenofovir	Previous (emtricitabine + tenofovir) → lopinavir/ritonavir [¶] + didanosine + abacavir Previous (lamivudine + abacavir) → lopinavir/ritonavir [¶] + zidovudine + tenofovir	
Most likely second-line antiretroviral therapy – when first-line PI based*			
< 3 years	> 3 years but < 30 kg	> 30 kg	> 40 kg
Nevirapine + zidovudine + didanosine	Efavirenz + zidovudine + didanosine	Efavirenz + zidovudine + tenofovir	Previous (emtricitabine + tenofovir) → efavirenz + didanosine + abacavir Previous (lamivudine + abacavir) → efavirenz + zidovudine + tenofovir

*At failure undertake review of adherence and resistance testing. Ideally children should not remain on failing regimens for prolonged periods, because of the risk of accumulating resistance mutations. Second-line ART choices should always be guided by resistance test results.

[†]Some clinicians use four-drug combination therapy (zidovudine + lamivudine + abacavir + nevirapine) for starting treatment in infants with very high HIV viral loads, not all clinicians agree that this is necessary, a randomised controlled trial is underway which will help to address this further (the Arrow trial www.arrowtrial.org/).

[‡]Where there are concerns about optimal adherence, it is advisable to start with a boosted PI regimen and monitor drug levels. When the HIV VL is consistently < 50copies/ml, then change to once daily NNRTI regimen can be offered.

[§]Fixed dose combinations ("Truvada" – emtricitabine + tenofovir, "Kivexa" – lamivudine + abacavir).

[¶]Alternative PIs include atazanavir/r, fosamprenavir/r, saquinavir/r and darunavir/r.

^{||}tenofovir may be substituted for didanosine.

*Failure of a boosted-PI regimen is particularly likely to be due to adherence rather than resistance, and this must be addressed before switching to an NNRTI. Tenofovir is not licensed for use in children.

possible cardiovascular toxicity of ABC in adults while on ABC [34–36] remains controversial. Most physicians now avoid ABC in adult patients at high risk of cardiovascular disease. However, cardiovascular risk is very low in children and although the place of ABC as first-line ART for children may need further consideration if more data become available, it currently remains appropriate; indeed ABC may be best used early in life before cardiovascular risk increases. 3TC and ZDV can be used in children with the HLA genotype B*5701 who are at high risk for ABC hypersensitivity reactions. Tenofovir is not licensed for children, and there are concerns about potential renal toxicity and effects on bone mineralization in prepubertal children which need to be answered. It should not be used together with ddI. It can be used in adolescents, who could also benefit from taking *Atripla* (EFV/tenofovir/FTC), a once-daily FDC, which is recommended first-line in adults (although not licensed until the VL is fully suppressed) [2].

Other FDCs are *Truvada* (Tenofovir/FTC) and *Combivir* (ZDV/3TC). FDC formulations should be used wherever possible to reduce pill burden. The choice of NRTI backbone will be different for children with HBV co-infection.

Some clinicians choose to use three NRTIs with an NNRTI or PI, or two NRTIs with both a PI and NNRTI [37] in infants because of high VLs and the risk of encephalopathy in this age group, but there are no trial data to support this.

6.3. Choice of accompanying drug class with NRTI backbone for first-line ART – NNRTI or PI?

The choice of whether to add a PI or NNRTI to the dual NRTI backbone is being addressed in PENPACT 1, a 4-year randomized trial of 263 children with a VL endpoint, finishing in 2009 (see www.pentatrials.org/). Currently either an NNRTI or a PI is acceptable. Issues to consider include: age appropriate formulations; palatability, which

may be a particular problem with RTV-containing syrups; frequency of daily dosing; and likely adherence. Another consideration is to try to match the half-life with the nucleoside backbone – e.g. EFV which has a long half-life, combined with the long half-life tenofovir and FTC; a PI combined with ZDV and 3TC or 3TC and ABC which have shorter half-lives. For EFV and NVP, single point mutations in the reverse transcriptase gene may lead to virological failure and resistance to both drugs; complete NNRTI resistance can therefore develop after only a few missed doses. Families should be counselled carefully about these issues prior to starting ART. A PI-based regimen may be favoured in children or adolescents in whom adherence is predicted to be poor.

6.4. Which NNRTI?

The choice currently is between EFV and NVP. The correct EFV dose has not been determined in children <3 years and NVP must be used in this age-group. The 2NN study showed similar efficacy of NVP and EFV in adults [38], but because of the increased risk of NVP hypersensitivity reactions (especially at high CD4 cell counts in adults) and concerns about the efficacy of once-daily NVP dosing, most adult guidelines prefer EFV. An EFV syrup is available, but because of reduced bioavailability, care must be taken as the liquid dose is larger than the capsule dose. Although limited, paediatric data on EFV-containing combinations show good efficacy. The main concern is neuropsychological side effects of bad dreams, mood swings and drowsiness, which anecdotally may be worse in older children, and are a reason for avoiding the drug in children with any underlying psychological disturbance. EFV is contraindicated in pregnancy and care needs to be taken when prescribing to post-pubertal girls. A rash is much less common with EFV than with NVP, and a rash with one NNRTI does not preclude using the other.

The most important side effects of NVP are: skin rash, fulminant hepatitis and Stevens–Johnson syndrome. A rash is relatively common but the last two have rarely been reported in children, in whom toxicity overall appears to be less common than in adults [39]. A rash and hepatic dysfunction are less common when a 2-week half-dose lead-in dosage is used. The use of body surface area dose calculations (ensuring minimum dose of 300 mg/m²/day given BID) which may be converted to weight band tables (see WHO guidelines [3]) has improved the previous confusion about dosing as mg/kg in which a sudden ‘step-down’ of dose occurred at age 7 years.

Etravirine (TMC 125) is a new twice-daily NNRTI which is entering Phase II trials in children. It is not fully cross-resistant with NVP/EFV but once more than two NNRTI

mutations are present its efficacy significantly decreases [40]. The next generation drug, TMC 278 (once daily), is in trials in adults.

6.5. Which PI?

Based on extrapolation from adult data, PI use in children should be RTV-boosted to optimize drug levels. The higher drug levels achieved with RTV boosting lead to improved virological suppression and reduced resistance; currently these advantages outweigh the increased risks of abnormal lipids and drug interactions. The question of which PI should be used is based on balancing pill burden, toxicity, experience and available data. There are most data on lopinavir/r (*Kaletra*) in children [41], which is also the only combined formulation with both lopinavir and RTV in the same tablet or liquid. In addition to adult heat stable tablets (lopinavir 200 mg/RTV 50 mg) and the liquid formulation (lopinavir 80 mg/RTV 20 mg/mL, low volume but unpleasant taste), heat stable paediatric tablets are now available (lopinavir 100 mg/RTV 25 mg); note, the tablets cannot be broken or crushed as bioavailability is lost. Unboosted PIs, such as nelfinavir (NFV), are no longer recommended.

Atazanavir/r, fosamprenavir/r, darunavir/r and saquinavir/r have comparable efficacy with lopinavir/r in adults. Fosamprenavir/r and darunavir/r are licensed for children from age 6 years in Europe. Atazanavir/r has a paediatric licence in the United States, and may be licensed for children in Europe in 2009 or 2010. Lopinavir/r remains the drug of choice for infants and young children (<6 years). For teenagers atazanavir/r may be preferable because it has the advantage of once-daily dosing, however they must be warned that jaundice may occur. When drugs show comparable toxicity and efficacy profiles, responsible clinicians need to be aware of the local prices of the different drugs available

6.6. Drug Dosing

Drug dosing and other information are summarized in Table 3, and given in more detail at www.pentatrials.org, where drug sheets will be updated as information changes.

7. Monitoring on ART

- The aim of ART is to achieve an undetectable viral load (<50 copies/mL plasma) and CD4 reconstitution; VL and CD4 cell count should be monitored approximately every 3 months once established on ART.

Table 3 PENTA 2009 Paediatric HIV Drug Dosing Chart

Agent	Recommended Dosage and Important Side Effects	Formulation	Comment	Intake Advice
Nucleoside Reverse Transcriptase Inhibitors (NRTI): <i>lactic acidosis, steatosis, lipodystrophy (effects of mitochondrial toxicity)</i>				
Abacavir (ABC) <i>Ziagen^R (GSK)</i>	Child: (≥ 3 months): 8 mg/kg BD. (max. dose 300 mg BD) 300 mg tablets: (14–21 kg): 1 tablet daily; (21–30 kg): 1½ – tablets daily; (> 30 kg): 2 tablets daily (may be given in 2 divided doses instead of once daily) Adult: (≥ 12 years): 300 mg BD or 600 mg OD Hypersensitivity reactions (usually within first 6 weeks of therapy) require careful evaluation. If proven, not to be given again (rare in Afro-Caribbeans). HLA-B*5701 test before starting Nausea, fever, headache, diarrhoea, rash, fatigue, respiratory symptoms.	Tab: 300 mg (yellow) scored Liquid: 20 mg/mL (2 month expiry)	See Table S1 for data on once-daily dosing in children ≥ 3 years. Once-daily dosing in younger children is under investigation	Can be given with food. Can be crushed and mixed with small amount of water or food.
Didanosine (ddI) <i>Videx^R (BMS)</i>	Child: (2 weeks – 3 months): 50–100 mg/m ² BD; (> 3 months): 200 mg/m ² OD – range 180–240 mg/m ² OD Adult: (< 60 kg): 250 mg OD; (> 60 kg): 400 mg OD Peripheral neuropathy, pancreatitis, nausea, diarrhoea. Lipodystrophy, lactic acidosis and pancreatitis enhanced in combination with stavudine.	Enteric coated caps: 125/200/250/400 mg (white) Chewable/Dispersible Buffered Tabs 25, 50, 100, 150 and 200 mg Powder for oral solution 10 mg/mL (refrigerate, stable for 30 days) Buffered powder for oral solution 100, 167 and 250 mg	Not recommended with tenofovir. Powder for oral solution reconstituted with water and <i>Mylanta Extra</i> strength or <i>Maalox Plus</i> antacid suspensions	Give on empty stomach (2 h after and 1 h before food or milk). Caps can be opened and sprinkled on a spoonful of food e.g. yogurt but decrease in AUC (see Table S1).
Emtricitabine (FTC) <i>Emtriva^R (Gilead)</i>	Child: oral solution (≥ 4 months) 6 mg/kg OD oral solution (max. dose 240 mg OD) Adult: Capsule (≥ 33 kg) 200mg OD; oral solution: 240 mg OD Headache, diarrhoea, nausea, rash, skin discolouration on palms and soles (more prominent in non-Caucasians), exacerbations of hepatitis B on discontinuation.	Cap: 200mg (blue/white) Liq: 10mg/mL – Fridge (Discard 45 days after opening) Not bioequivalent to caps	Reduce dose in renal impairment.	Can be administered with food.
Lamivudine (3TC) <i>Epivir^R / Zeffix^R (GSK)</i>	Neonate: (age ≤ 30 days): 2 mg/kg BD. Child: 4 mg/kg BD. (max. dose 150mg BD) Adult: (≥ 12 years) 150 mg BD or 300 mg OD Nausea, diarrhoea, headache, fatigue, exacerbations of hepatitis B on discontinuation.	Tab: 100 mg (<i>Zeffix</i>) (orange) 150 mg (<i>Epivir</i>) (white) scored 300 mg (<i>Epivir</i>) (grey) Liq: 10 mg/mL (<i>Epivir</i>) (30 day expiry)	See Table S1 for data on once-daily dosing in children ≥ 3 years. Once-daily dosing in younger children is under investigation	Can be given with food. Can be crushed and mixed with small amount of water or food.
Stavudine (d4T) <i>Zerit^R (BMS)</i>	Neonate: (age ≤ 13 days): 0.5 mg/kg BD. Child: (< 30 kg): 1 mg/kg BD; (30–60 kg): 30 mg BD. Adult: (30–60 kg): 30 mg BD; (> 60 kg): 40 mg BD Peripheral neuropathy, pancreatitis, hepatitis, gastrointestinal disturbances, headache, rash. Lipodystrophy, lactic acidosis and pancreatitis enhanced in combination with didanosine.	Caps: 15 mg (red/yellow), 20 mg (orange) 30 mg (yellow/orange) 40 mg (brown) Liq: 1 mg/mL (refrigerate, stable for 30 days)	Not to give with AZT	Can be administered with food.
Zidovudine (AZT, ZDV) <i>Retrovir^R (GSK)</i>	Child: 180 mg/m ² BD. (max. dose 300 mg BD) or (≥ 4 kg to < 9 kg): 12 mg/kg twice daily (max 300 mg twice daily); (≥ 9 kg to < 30 kg): 9 mg/kg twice daily (max 300 mg twice daily); Adult: 250 mg BD (300 mg BD for <i>Combivir</i> or <i>Trizivir</i> combinations). Granulocytopenia and/or anaemia, nausea, headache, myopathy, hepatitis, nail pigmentation, neuropathy	Cap: 100 mg (white)/ 250 mg (white/blue) Liq: 10 mg/mL – Sugar free (30 day expiry) IV infusion: 10 mg/mL	Not to give with d4T	Can be given with food. Capsules can be opened and dissolved in water.

Table 3 Continued

Agent	Recommended Dosage and Important Side Effects	Formulation	Comment	Intake Advice
ABC + 3TC <i>Kivexa^R (GSK)</i>	Child: individual ABC & 3TC dose BD – max. dose as for adults Adult (≥ 40 kg): 1 tablet OD	Tab: ABC 600 mg/3TC 300 mg (orange)	Can be cut	Can be administered with food.
AZT + 3TC <i>Combivir^R (GSK)</i>	Child: individual AZT & 3TC dose BD – max. dose as for adults Adult (≥ 30 kg): 1 tablet BD	Tab: AZT 300mg/3TC 150 mg (white), scored	Can be cut	Can be administered with food.
ABC + 3TC + AZT <i>Trizivir^R (GSK)</i>	Child: individual ABC, 3TC & AZT – max. dose as for adults Adult (≥ 18 years): 1 tablet BD	Tab: AZT/ABC/3TC 300/300/150 mg (green)	Not to be cut	Can be administered with food.
Nucleotide Reverse Transcriptase Inhibitors (NRTI): As NRTIs				
Tenofovir (TDF) <i>Viread^R (Gilead)</i>	Child: (2–8 years): 8 mg/kg OD; (> 8 years): 210 mg/m ² OD – Limited data see info sheet. (max. dose 300 mg OD) Adult: (> 18 years): 300 mg OD. All doses based on Tenofovir DF. Headache, nausea, vomiting, renal tubular dysfunction, bone demineralization, exacerbations of hepatitis on discontinuation. Important: Renal function, blood and urine monitoring	Tab: TDF 300 mg (blue)	Not recommended with ddl Dose reduction in renal impairment	Can be administered with food. Can disperse in water or juice.
TDF + FTC <i>Truvada^R (Gilead)</i>	Child: individual TDF & FTC – max. dose as for adults Adult (> 18 years): 1 tablet OD	Tab: TDF/FTC 300/200 mg (blue)	Can be cut	Can be given with or without food.
TDF + FTC + EFV <i>Atripla^R (Gilead/BMS)</i>	Child: individual TDF, FTC & EFV – max. dose as for adults Adult (> 18 years): 1 tablet OD	Tab: TDF/FTC/EFV300/200/600 (pink)	Do not cut	Give on empty stomach (2 h after food).
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI): Do TDM for both NNRTIs and PIs in combination. Do TDM with Rifamycins. Long half life consider cover with PI after stopping				
Efavirenz (EFV) <i>Sustiva^R (BMS)</i> <i>Stocrin^R (MSD)</i>	Child: (3–5 years liquid only): (13–15 kg): 360 mg, (15–20 kg): 390 mg, (20–25 kg): 450 mg, (15–32.5 kg): 510 mg. (≥ 5 years): (13–15 kg): 200 mg OD (liq: 270 mg); (15–20 kg): 250 mg OD (liq: 300 mg); (20–25 kg): 300 mg OD (liq: 360 mg); (25–32.5 kg): 350 mg OD (liq: 450 mg); (32.5–40 kg): 400 mg OD (liq: 510 mg) Adult: (> 40 kg): 600 mg OD (liq: 720 mg) NB: tablet/capsule NOT bioequivalent to liquid Mood changes, vivid dreams (common but usually short lived), hypercholesterolemia, rash.	Cap: 50 mg (yellow/white) 200 mg (yellow) Sustiva tabs: 600 mg (yellow) Stocrin tab: 50 mg (yellow) 200mg (yellow), 300 mg (white), 600 mg (yellow). Liq: 30 mg/mL Not bioequivalent to tablets or capsules	No dose adjustments in renal impairment necessary. Tablet can be cut	Preferably given before bedtime. Capsules can be opened and added to liquids or a small amount (1–2 teaspoons) of food.
Etravirine (ETR, TMC 125) <i>Intelence^R(Tibotec, Janssen-Cilag)</i>	Child: 5.2 mg/kg currently under investigation (see Table S1) Adult: 200 mg BD Diarrhoea, flatulence, abdominal pain, headache, pruritis, rash. Rash usually resolves in 1–2 weeks	Tab: 100 mg tablet (white) 25 mg tablet on compassionate use	AUC decreased by 50% if taken on empty stomach	Take with food. Tablet disperses in water.
Nevirapine (NVP) <i>Viramune^R (Boehringer Ingelheim)</i>	Child: (> 14 days): 150–200 mg/m ² OD for 2/52, then 150–200 mg/m ² BD (max. dose 200 mg BD) Adult: 200 mg OD for 14 days, then increase to 200 mg BD if no rash or LFTs abnormalities Rash, hepatitis, Stevens–Johnson syndrome – usually first 12 weeks. Monitor liver function prior to initiating therapy and at frequent intervals	Tab: 200 mg (white) scored Liq: 10 mg/mL (shake well). Six months expiry	No dose adjustments in renal impairment necessary	Can be administered with food.

Table 3 Continued

Agent	Recommended Dosage and Important Side Effects	Formulation	Comment	Intake Advice
Protease Inhibitors (PI): Lipodystrophy, hyperlipidaemia, diabetes mellitus, important interactions with a range of other drugs. If on dual PI, NNRTI or TB therapy need TDM				
Atazanavir (ATV) <i>Reyataz^R</i> (BMS)	Child: (15–25 kg): 150 mg OD with RTV 80 mg OD; (25–32 kg): 200 mg OD with RTV 100 mg OD; (32–39 kg): 250 mg OD with RTV 100 mg OD; (≥ 39 kg): 300 mg OD with RTV 100 mg OD Adult: 300 mg OD with RTV 100 mg OD Nausea, headaches, rash, jaundice and elevated total bilirubin	Caps: 100 mg (dark blue/white) 150 mg (dark blue/light blue) 200 mg (dark blue) 300 mg (red/dark blue)	Omeprazole and all other PPIs are contraindicated	Give with food. Avoid indigestion remedies.
Darunavir (DRV, TMC 114) <i>Prezista^R</i> (Tibotec-Janssen-Cilag)	Child: (> 6 years): (20–30 kg) 375 mg darunavir BD plus 50 mg ritonavir BD; (30–40 kg) 450 mg darunavir BD plus 60 mg ritonavir BD; (> 40 kg) 600 mg darunavir BD plus 100 mg ritonavir BD. Adult: ART experienced: 600 mg BD + RTV 100 mg BD. ART naïve: 800 mg OD + RTV 100 mg OD Rash, nausea, diarrhoea, headache. Contains sulphamide moiety – check allergies	Tab: 75 mg, 150 mg, 400 mg, 600 mg	Liquid formulation under investigation	Give with or after food.
Fosamprenavir (FPV) <i>Telzir^R</i> (GSK)	Adults (> 18 years): (Tablet or oral suspension) 700 mg fosamprenavir BD with 100 mg ritonavir BD Child (2–5 years): 30 mg/kg BD; (≥ 6 years): (25–32 kg): 18 mg/kg BD with ritonavir 3 mg/kg BD; (33–38 kg): (Tablet or oral suspension) 18 mg/kg BD with 100 mg ritonavir BD; (≥ 39 kg): (Tablet or oral suspension) 700 mg fosamprenavir BD with 100 mg ritonavir BD. Max 700 mg BD. Rash, perioral paraesthesia, nausea, diarrhoea.	Tab: 700 mg (pink) Liq: 50 mg/mL 28 day expiry. Taken with food to aid palatability and adherence.	Complex drug interactions with Kaletra	Give with or after food to aid palatability of liquid. Tablets – take without food.
Lopinavir/r (LPV/r) <i>Kaletra^R</i> (Abbott)	Neonate/Infant: (≥ 14 days–6 months): 300 mg/m ² BD. Child: (≥ 2 years): 230 mg/m ² BD Without EFV/NVP: (0.6–0.9 m ²): 200 mg BD; (0.9–1.4 m ²): 300 mg BD; (≥ 1.4 m ²): 400 mg BD With EFV/NVP: 300/75 mg/m ² (max 500 mg/125 mg) twice a day dose. 300 mg/m ² $\text{dose in mL} = \frac{300 \times \text{Surface area}}{80}$ 230 mg/m ² $\text{dose in mL} = \frac{230 \times \text{Surface area}}{80}$ Adult: 400 mg BD = 2 tabs BD = 4 paed tabs BD = 5 mL BD of solution ' All doses based on LPV ' Cautious use with hepatic insufficiency. Diarrhoea, headache, nausea, vomiting	Tab: 200mg LPV /50mg RTV (yellow) Tab (paed): 100mg LPV/ 25mg RTV (yellow) Liq: 5ml = 400mg LPV / 100mg RTV (yellow) – Fridge Cap: 133.3mg LPV/33.3mg RTV (orange) - No longer available in some countries	The licensed 230mg/m ² leads to lower trough levels in children, some clinicians may consider using 300mg/m ² BD	Cap & Liq: Give with or after food. Tab: Can be given with or without food (no data in < 18 years of age).
Ritonavir (RTV) <i>Norvir^R</i> (Abbott)	Child: For boosting other PIs see specific drug. <i>Not recommended as a single PI.</i> Adult: For boosting other PIs: 100 mg BD or 100 mg OD e.g. with ATV or 200 mg BD with TPV Perioral paraesthesia, nausea, diarrhoea, flushing, rash, hepatitis B with treatment dose	Caps: 100 mg (white) – Store in fridge Liq: 80 mg/mL (contains 42% ethanol) – Store at room temp		Give with or after food. Can mask bitter taste with chocolate milk (see sheet).

Table 3 Continued

Agent	Recommended Dosage and Important Side Effects	Formulation	Comment	Intake Advice
Saquinavir (SQV) <i>Invirase^R (Roche)</i>	Child: Insufficient data - seek specialist advice Adult: 1g BD with RTV 100mg BD Diarrhoea, nausea, rash, exacerbation of chronic liver disease	Tab: 500 mg (brownish-orange) Cap: 250 mg (brown & green)	Tablets can be cut	Absorption significantly increased with food.
Tipranavir (TPV) <i>Aptivus^R (Boehringer)</i>	Child: (2-18 years): 14 mg/kg BD with RTV 6 mg/kg BD or 375 mg/m ² BD with RTV 150 mg/m ² BD Adult: 500 mg BD with RTV 200 mg BD Liver toxicity (monitor), rash, nausea, diarrhoea. Reports of intracranial haemorrhage. Contraindicated in patients with moderate to severe hepatic insufficiency. Contains sulphonamide moiety - check allergies	Caps: 250 mg (pink) contain 7% ethanol. Refrigerate. Discard 60 days after opening. Liquid: Available in US. Store at room temp. Discard 60 days after opening	Complex interactions Reduced levels with ABC and AZT	Give with or after food.
Fusion & Entry Inhibitors				
Enfuvirtide (T-20) <i>Fuzeon^R (Roche)</i>	Child: (6-16 years): 2 mg/kg BD sub-cut. (max. dose 90 mg BD) Adult: 90 mg BD sub-cut Local injection site reactions common, less common bacterial pneumonia	Inj: 108 mg/1.1 mL vial for subcutaneous injection (90 mg/1 mL) Clear		Subcut injection (upper arm, thigh, abdomen) - see product information.
Maraviroc (MVC) <i>Celsentr^R (Pfizer)</i>	Child: Insufficient data - seek specialist advice Adult: 150 mg BD (with CYP3A40 inhibitor), 600 mg BD (with CYP3A40 inducer), 300 mg BD (with NVP) 'TROFILE^R ASSAY FOR CO-RECEPTOR TROPISM' Nausea, constipation, headache, dizziness, pruritus	Tabs: 150mg, 300mg (blue)	Pharmacy advice on dosing with potentially interacting agents	With or without food.
Integrase Inhibitors				
Raltegravir (RAL, MK518) <i>Isentress^R (MSD)</i>	Child: Insufficient data - seek specialist advice Adult: (≥ 16 years): 400 mg BD Nausea, dizziness, insomnia, rash, pancreatitis, elevated ALT, AST, Gamma GT	Tabs: 400 mg tabs (pink)	CYP450 and P-gp interactions unlikely. Avoid indigestion remedies	With or without food.
Prophylaxis				
Co-trimoxazole <i>Septrin^R (GSK)</i> <i>Bactrim^R (Roche)</i>	<i>PCP prophylaxis - Suggested regimen OD 3 x weekly. See Table S1 for alternative regimens.</i> Child (from age 1 month): (<0.25 m ²): 120 mg; (0.25-0.39 m ²): 240 mg; (0.4-0.49 m ²): 360 mg; (0.5-0.75 m ²): 480 mg; (0.76 -1 m ²): 720mg; (> 1 m ²): 960 mg	Tab: 480 mg, 960 mg (white) Liq: 240 mg/5 mL (paed) 480 mg/5 mL (adult)		Can be administered with food.

Important notes: To ensure accurate dosing always use oral syringes to measure liquid medicines. Doses are not necessarily manufacturers' recommended dose and may not be licensed in children (see Table S1). Doses may change - please check. Always check potential drug interactions with concomitant therapy (see www.hiv-druginteractions.org). Currently TDM available for most PIs and NNRTIs but not NRTIs. This table was prepared as the consensus view of the PENTA Guidelines Writing Group on 22 May 2009. The table is intended to be used in conjunction with the detailed antiretroviral drug sheets (see www.pentatrials.org) by practitioners experienced in paediatric HIV care. Please do not use this outside these recommendations as dosing information is rapidly evolving and may change. Surface area may be calculated according to the formula below or looked up according to weight (see Sharkey *et al.*, *Br J Cancer* 2001; **85**(1): 23-28.

$$BSA(m^2) = \sqrt{\frac{\text{height(cm)} \times \text{weight(kg)}}{3600}}$$

- More frequent clinical and laboratory monitoring is required in infancy, if adherence is poor, soon after starting or changing therapy and when giving other medications such as antituberculous therapy.

Clinical and laboratory monitoring requirements for children on ART are similar to those of ART-naïve children. In addition to the routine clinical, growth, development and laboratory monitoring described in section 3, it is important to check specifically for adherence to therapy, and for side effects. Monitoring needs to be more frequent in infancy and shortly after initiating or changing therapy, but once children are established on treatment and stable, clinic visits can be 3 monthly.

TDM of NNRTIs and PIs is available in several quality-controlled laboratories in Europe. There are no studies to inform recommendations for routine use of TDM in all children, but it may be particularly useful where there is a suspicion of: (1) drug toxicity; (2) poor adherence; (3) drug interactions (e.g. TB treatment); (4) failure to suppress viraemia despite apparent good adherence; (5) renal or hepatic dysfunction; or (6) use of unlicensed dosing regimens. TDM may also be considered in infants and neonates, where pharmacokinetic data are less well established. TDM is generally not indicated for NRTIs as intracellular levels of the active metabolite are complex to measure and require large blood volumes.

8. Adherence and disclosure

- Drug adherence is of paramount importance and should be discussed at each clinic visit.
- Disclosure to a child of their HIV diagnosis at the appropriate age should be promoted.

Optimal adherence to treatment is of paramount importance for long-term efficacy of ART, and children rely on caregivers to deliver this. Although there are some data on the predictors of adherence, there are few studies of successful interventions to improve adherence; nor is there a gold standard for measuring adherence. A recent review of over 50 studies in paediatric HIV infection identified several factors related to drug regimen, child and family which predicted paediatric adherence to ART [42]. Not surprisingly, number of daily doses, age, awareness of diagnosis, beliefs about impact of medication on daily life, social stresses and child or adult responsibility for giving medication were all found to be important. Most of these factors are outside the control of the treating clinician, but should be acknowledged and addressed. Factors which may be influenced by the medical team include once-daily

medication regimens and choice of formulation. Despite the difficulties and lack of easy solutions, the issue of adherence should always be addressed before and after starting children on ART. It is acknowledged that adherence issues change with age and may be particularly difficult in adolescents.

Children's knowledge of their illness should be assessed and an age-appropriate process of gradual disclosure started. Increasingly, most clinicians now address issues of disclosure at an earlier age than previously, with an awareness that early, general discussions focusing on healthy living, and knowledge about the blood and immune system can provide a useful foundation for later, specific discussions about HIV. It will generally be appropriate for most children to know their HIV status (i.e. have named the disease) before teenage years (i.e. from age 9 to 10), although timing of disclosure will vary according to the young person's pre-existing knowledge, maturity and carers' wishes. Young people's awareness of their HIV status may have an impact on adherence. Issues around safe sex and contraception should be continually addressed, giving young people an opportunity to speak with clinic staff on their own if they wish. The provision of services appropriate to adolescents with perinatally acquired HIV, and the managed transition of their care to adult services are increasingly important.

9. Drug toxicities and interactions

- Toxicities depend on the individual drugs and ART combination and should be assessed at each clinic visit.
- Drug interactions should be considered when starting new medications in a child on ART.
- Use websites to check drug interactions and toxicities.

Drug toxicity has been the major limitation of ART to date, and one of the aims of modern ART regimens is to reduce side effects. Detailed side effects of individual drugs are discussed in Table S1 (see Supporting Information). Some adverse effects, such as lipid derangements and hepatitis, may be as a result of either ART or HIV itself. The SMART study in adults has been important in demonstrating that treatment with ART results in fewer such problems than withholding drugs [21].

In the short term, adherence may be affected by common side effects which are not dangerous but cause significant disturbance to daily life – e.g. diarrhoea due to lopinavir/r, dysphoria caused by EFV, nausea or headache due to ZDV. A rare but clinically important early side effect is ABC hypersensitivity, which may be fatal if the drug is re-

introduced after a reaction. Children with HLA-B*5701 should not be given ABC; the Predict study in adults provides compelling evidence that screening should be adopted as routine practice where possible [11].

One effect of starting ART may be Immune Reconstitution Inflammatory Syndrome (IRIS). This occurs a few weeks after starting therapy. It is not specific to any drug, but represents worsening of symptoms as immune responses improve after successful treatment.

In the longer term, lipodystrophy was historically one of the most important side effects limiting treatment acceptability to patients. This is much rarer now in regimens avoiding the use of d4T, especially combined with ddI and/or PIs. Other metabolic disturbances include mitochondrial toxicity, elevated cholesterol and triglycerides, and altered glucose homeostasis [43]. Some studies have shown an increase in markers of cardiovascular risk such as carotid intimal thickness; however, it is unclear from cross-sectional data how much this relates to ART or HIV disease [44]. In the SMART trial, cardiovascular events were more common in adults undergoing treatment interruptions than on continuous ART. An important long-term toxicity being evaluated in an ongoing Phase II trial is the effect of tenofovir on renal function and bone mineralization in children. Results are likely to be available by 2010; this is important as tenofovir is widely used as a first-line agent in adults. For all drugs, the effects of prolonged use for decades remain to be seen, and this will be of great significance as more children start ART earlier.

10. Stopping treatment and treatment interruptions

- Treatment interruptions cannot be recommended and starting ART currently means lifelong therapy.
- If stopping NNRTIs, this requires a substitution or staggered stop to reduce the risk of developing NNRTI resistance.

Earlier ART initiation in children and ART for all those diagnosed during infancy increases the importance of addressing the question of whether ART needs to be given lifelong with no interruptions, or whether children treated early with superior thymic function to adults could recover immune function, and undergo periods off ART. Potential benefits of planned treatment interruptions in children include reduced cumulative drug toxicity, reduced viral resistance as a result of reduced drug exposure, better adherence during periods when ART is taken and improved quality of life. The results of most adult interruption trials

have not been encouraging; in particular the occurrence of higher rates of non-AIDS serious cardiovascular, renal and hepatic toxicities in adults when they came off therapy suggested that these events were related to inflammation from HIV rather than ART [21].

Largely because of the SMART trial results, treatment interruptions are no longer recommended in adult patients being treated successfully. However, the median age of participants in SMART was 44 years, with 75% of participants aged 38 years or more. It is unlikely that children would have the same short- or medium-term risks, although long-term risks may be higher. Studying the possibility of treatment interruption therefore remains attractive. The pilot PENTA 11 randomized trial showed no deaths or progression to AIDS after CD4-guided planned treatment interruptions, but long-term follow-up of children in PENTA 11, who are now all back on treatment, as well as results of larger ongoing studies (BANA in Botswana; CHER in South Africa) are needed before further recommendations can be made [45]. Future guidance will incorporate evidence from these studies. In the meantime, treatment interruptions cannot be recommended and starting ART currently means lifelong therapy.

Despite this recommendation for continuous therapy, children do sometimes stop ART (e.g. for adherence difficulties). Where possible, this should be done safely to avoid development of resistance to classes of drugs which could be used again in the future. Recent evidence from a sub-study of PENTA 11 which measured drug levels, VL and resistance after stopping NVP and EFV-based ART, provides recommendations on strategies to avoid development of NNRTI resistance when stopping ART regimens containing these drugs [46]. The options are a 'staggered stop', where the NRTI backbone is continued for 7–10 days after stopping the NNRTI to cover the 'tail', or a 'replacement stop', where the NNRTI is replaced by a boosted PI before discontinuing the PI and NRTIs simultaneously. Either strategy may be used for NVP, although a 7–10 day replacement stop may be preferred. EFV metabolism is more variable, and its 'tail' may be longer. A staggered stop is therefore NOT recommended for EFV, and the replacement stop needs to be longer (21 days of PI and NRTIs) [46].

11. When to switch ARV drugs

- The best time to switch remains uncertain pending the results of PENPACT 1.
- Switching treatment when there are ongoing problems with adherence may lead to loss of efficacy of further classes of ART.

- Where there are blips in VL, blood tests should be repeated to confirm significance.

ART regimens may be changed during successful treatment (simplification) or because of treatment failure. Treatment simplification may involve reducing the number of drugs (e.g. from 4 to 3) or tablets as a child becomes older, changing from twice- to once-daily therapy, or changing from initial boosted PI-based regimens to NNRTI-based regimens once viral suppression is achieved and adherence is assured. Simplification should not be carried out with significant detectable viraemia because of the risk of selecting for resistant virus. Reducing the number of drugs below a standard three-drug regimen is not currently recommended outside clinical trials.

In virological failure, adult practice is to switch ART early if there is detectable viraemia, because of the risk of accumulation of resistance mutations, which may make subsequent regimens less effective. This logic also applies to children, although to date no trials have reported randomized evidence on 'when to switch' in either adults or children (PENPACT 1 finishes in 2009 and is the only ongoing trial worldwide addressing the question of VL threshold for switching, see www.pentatrials.org). Virological failure precedes immunological and clinical failure and in children is frequently the result of poor adherence. In children, switching therapy should only be considered when adherence has been reviewed. Children's adherence is not constant and often changes with age, and with life events such as puberty or learning their HIV diagnosis. Changing drug regimens with no improvement in adherence may simply result in rapid development of resistance to the new drugs. Considering the length of time they are likely to require treatment, it is important that children have not 'burnt' all ART options before they reach young adulthood. Alternatives to early switching are to stay on the same regimen while working to improve adherence, or to stop ART temporarily if clinical status and CD4 cell count permit, until a new regimen can be started with better predicted adherence.

In the past, with a paucity of drugs available to children, paediatricians and families have been relatively conservative about switching based on detectable viraemia. Children can remain clinically and immunologically stable for a considerable period in the presence of viraemia and caregivers as well as paediatricians may be reluctant to switch ART. Analysis of the UK/Irish cohort showed a median time on first-line ART of approximately 7 years in the past (1997–2005) although most children switched ART with VL between 1000 and 30 000 copies/mL, no clear level was identified [47]. With increasing numbers of drugs available, the rationale for such an approach is now diminishing. Indeed,

the importance of preventing mutations with potential cross resistance against newer drugs is an increasingly apparent reason for not tolerating persistent viraemia in the presence of failing ART. Of note, as in adults, single VL blips (single VL values >400 but <1000 copies/mL) do not predict subsequent virological failure, but these should always be followed up as soon as possible, to make sure that they are not the beginning of significant viral rebound [48].

12. Resistance testing and second and subsequent ART regimens

- Resistance testing should be performed prior to switching regimens.
- Expert interpretation of resistance tests is required.
- Substituting single drugs in a failing regimen should be avoided.

Adding or substituting single drugs in a failing ART regimen without resistance testing risks giving the new drug as effective monotherapy which may result in rapid development of further resistance. It is therefore recommended that all changes in therapy with detectable viraemia be preceded by a resistance test unless it is unequivocal that there is no cross-resistance with previous drugs received. Ideally resistance testing should be performed while the patient is still on the old regimen, or within a few weeks of stopping. Expert opinion should be sought in interpreting resistance genotypes. The general rule is to change all the drugs in the regimen after first-line ART failure with resistance. 3TC and ABC may be switched to ZDV and ddI or in adolescents, ZDV and tenofovir, which may be preferable as cross resistance may occur between ABC and ddI. Failure of an NNRTI-based regimen is often as a result of viral drug resistance, and switching to a boosted PI is appropriate. Failure of a boosted PI-based regimen is more likely to be because of poor adherence than resistance. If resistance is detected, a switch to an NNRTI-based regimen or another PI without overlapping resistance may be appropriate. If resistance is not detected, continuing the PI with enhanced adherence support should be considered. Any change in regimen should be preceded by a thorough re-assessment of adherence, and a plan for adherence monitoring of the new regimen.

Third and subsequent regimens are likely to be more complicated and need to take into account all previous drug histories and previous resistance results as well as the current regimen. This will always require expert input. In the future it may be possible to construct first-, second- and third-line ART regimens with little or

no cross-resistance of drugs. If this happens, the strategy for managing virological failure will need re-evaluation.

13. Coinfections

- Hepatitis B and C both increase the risk of hepatotoxicity with ART.
- Drugs used to treat hepatitis B may select for resistant HIV virus and vice versa.
- There is significant interaction between ART and TB therapy. ART may be deferred at higher CD4 cell counts, or rifampicin and PIs may be avoided if low CD4 cell count necessitates simultaneous treatment; use of rifabutin can be considered. Higher doses of ART with TDM may be needed.

13.1. Hepatitis B coinfection

In adults, there is well-documented interaction between HIV and hepatitis B (HBV) infection, with increased rates of liver disease. Long-term follow-up data for coinfecting children are sparse. With respect to ART, the most important consideration is that some, but not all, ARV drugs have activity against HBV (3TC, FTC, tenofovir). ART regimens in coinfecting patients should, where possible, contain drugs active against HBV, but treatment with 3TC or FTC without tenofovir may risk the evolution of resistant HBV. If HBV requires treatment in a patient whose HIV does not yet require treatment, then use of drugs also active against HIV (such as entecavir) without ART should be avoided to prevent development of HIV resistance. Seek expert advice for the appropriate management of coinfecting patients.

13.2. Hepatitis C coinfection

Hepatitis C (HCV) coinfection also increases the risk of liver disease, but long-term follow-up data for coinfecting children are sparse. No anti-HIV ART drugs are effective against HCV. However, there is an increased risk of hepatotoxicity with ARTs, which needs to be monitored, and ARTs may interact significantly with drugs used to treat hepatitis C, such as ribavirin. Seek expert advice for the appropriate management of coinfecting patients.

13.3. TB coinfection

There are particular difficulties of TB diagnosis, drug interactions and immune reconstitution disease in HIV-

infected children. The standard treatment with four antituberculous drugs is recommended, but rifampicin significantly interacts with NVP and PIs, generally reducing blood levels. Options are either to defer ART until TB treatment has been completed, or modify drug treatment. Rifabutin may be used instead of rifampicin to reduce interactions or EFV-based regimens or triple nucleoside regimens may be used. If rifampicin and EFV are used together, increased doses of EFV and TDM may be required. The relative timing of ART and antituberculous treatment depends on the degree of pre-ART immune suppression. With a CD4 count above 200 cells/ μ L, it may be possible to treat the TB first and start ART later. However, if the child has significant immune suppression and is at risk of disease progression, ART should not be delayed and a combination of rifabutin or rifampicin with NVP or EFV and two NRTIs, with close clinical supervision and drug level monitoring is advised. Useful information on drug interactions can be found at www.hiv-druginteractions.org. IRIS commonly occurs in children with TB, usually developing around 3–4 weeks after treatment with worsening of respiratory symptoms, particularly in children who have a low pre-ART CD4 cell count and high VL and starting ART within 2 months of starting TB treatment. ART should be continued, but steroids may be necessary to manage IRIS. Further details on management of ART and TB are found in the WHO guidelines [3].

14. Trials and research

This guideline remains largely based on expert opinion and the results of cohort studies. Some important RCT data have been incorporated, but ongoing enrolment of children into well-designed studies remains important and needs to be promoted whenever possible (see www.penta-trials.org).

15. Conclusion

ART options for children will continue to change, and the best way to use new drug classes should become apparent in the next few years. During the dozen or more years of effective HAART, HIV-infected children in Europe have become healthier and almost all are now surviving through adolescence and into adulthood. Over this time the management problems encountered by paediatricians have moved from treating sick young children to helping young people live as normal a life as possible with a chronic disease. Continued follow-up of these young people into adult life is essential in order to determine their long-term outcome, with particular regard to growth, neurocognitive function, fertility, malig-

nancy and long-term drug toxicity. Follow-up of the European cohort of long-term paediatric survivors will give very important information for the much larger cohorts of children now receiving treatment in resource-poor settings.

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Appendix

Table A1 CDC and WHO classifications

A1. WHO clinical staging of HIV/AIDS for children with confirmed HIV infection

World Health Organization. WHO Case Definitions of HIV for Surveillance, and Revised Clinical Staging and Immunological Classification of HIV Related Disease in Adults and Children. Geneva, World Health Organization, 2006

Clinical Stage 1

Asymptomatic
Persistent generalized lymphadenopathy

Clinical Stage 2

Unexplained persistent hepatosplenomegaly
Papular pruritic eruptions
Extensive wart virus infection
Extensive molluscum contagiosum
Fungal nail infections
Recurrent oral ulcerations
Unexplained persistent parotid enlargement
Lineal gingival erythema
Herpes zoster
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)

Clinical Stage 3

Unexplained* moderate malnutrition not adequately responding to standard therapy
Unexplained persistent diarrhoea (14 days or more)
Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month)
Persistent oral candidiasis (after first 6–8 weeks of life)
Oral hairy leukoplakia
Acute necrotizing ulcerative gingivitis/periodontitis
Lymph node TB
Pulmonary TB
Severe recurrent bacterial pneumonia
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including bronchiectasis
Unexplained anaemia ($<8\text{ g/dL}$), neutropenia ($<0.5 \times 10^9/l$) or chronic thrombocytopenia ($<50 \times 10^9/l$)

Clinical Stage 4[†]

Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
Pneumocystis pneumonia
Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)
Extrapulmonary/disseminated tuberculosis
Kaposi's sarcoma
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Central nervous system toxoplasmosis (after one month of life)
HIV encephalopathy
Cytomegalovirus infection retinitis or CMV infection affecting another organ, with onset at age over 1 month
Extrapulmonary cryptococcosis (including meningitis)
Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis, cryptococcosis)
Chronic cryptosporidiosis

Chronic isosporiasis
 Disseminated non-tuberculous mycobacteria infection
 HIV associated tumours including cerebral or B cell non-Hodgkin lymphoma
 Progressive multifocal leukoencephalopathy
 Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

*Unexplained refers to where the condition is not explained by other conditions.

†Some additional specific conditions can also be included in regional classifications (e.g. reactivation of American trypanosomiasis [meningoencephalitis and/or myocarditis] in Americas region, Penicilliosis in Asia and HIV-associated rectovaginal fistula in Africa).

A2. CDC 1994 REVISED CLASSIFICATION SYSTEM FOR HIV INFECTION IN CHILDREN LESS THAN 13 YEARS OF AGE [9]

Clinical Categories for Children with Human Immunodeficiency Virus (HIV) Infection

Category N: Not symptomatic

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in Category A

Category A: Mildly symptomatic

Children with two or more of the conditions listed below but none of the conditions listed in Categories B and C

- Lymphadenopathy (≥ 0.5 cm at more than two sites; bilateral = one site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

Category B: Moderately symptomatic

Children who have symptomatic conditions other than those listed for Category A or C that are attributed to HIV infection. Examples of conditions in clinical Category B include but are not limited to

- Anaemia (< 8 g/dL), neutropenia ($< 1.0 \times 10^9/L$), or thrombocytopenia ($< 100 \times 10^9/L$) persisting ≥ 30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (thrush), persisting (> 2 months) in children > 6 months of age
- Cardiomyopathy
- Cytomegalovirus infection, with onset before 1 month of age
- Diarrhoea, recurrent or chronic
- Hepatitis
- Herpes simplex virus (HSV) stomatitis, recurrent (more than two episodes within 1 year)
- HSV bronchitis, pneumonitis, or oesophagitis with onset before 1 month of age
- Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Persistent fever (lasting > 1 month)
- Toxoplasmosis, onset before 1 month of age
- Varicella, disseminated (complicated chickenpox)

Category C: Severely symptomatic

Serious bacterial infections, multiple or recurrent (i.e., any combination of at least two culture-confirmed infections within a 2-year period), of the following types:

- septicaemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)
- Candidiasis, oesophageal or pulmonary (bronchi, trachea, lungs)

- Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhoea persisting > 1 month
- Cytomegalovirus disease with onset of symptoms at age > 1 month (at a site other than liver, spleen, or lymph nodes)
- Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings):
 - (a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests;
 - (b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerised tomography or magnetic resonance imaging (serial imaging is required for children < 2 years of age);
 - (c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathological reflexes, ataxia, or gait disturbance
- Herpes simplex virus infection causing a mucocutaneous ulcer that persists for > 1 month; or bronchitis, pneumonitis, or oesophagitis for any duration affecting a child > 1 month of age
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi's sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunological phenotype
- *Mycobacterium tuberculosis*, disseminated or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Pneumocystis jirovecii* pneumonia (formerly *carinii*)
- Progressive multifocal leukoencephalopathy
- Salmonella (nontyphoid) septicaemia, recurrent
- Toxoplasmosis of the brain with onset at > 1 month of age
- Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings:
 - (a) persistent weight loss $> 10\%$ of baseline OR
 - (b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child ≥ 1 year of age OR
 - (c) < 5 th percentile on weight-for-height chart on two consecutive measurements, ≥ 30 days apart PLUS a) chronic diarrhoea (i.e., at least two loose stools per day for ≥ 30 days) OR b) documented fever (for ≥ 30 days, intermittent or constant)

Definitive diagnosis: microscopy (histology or cytology); culture; antigen detection.

Presumptive diagnosis: characteristic clinical presentation, supported by investigations other than microscopy or culture and after exclusion of other causes in the differential diagnosis.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Drug information.

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