Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial

*Paediatric European Network for Treatment of AIDS (PENTA)**

Summary

Introduction Treatment options for children with HIV-1 are limited. We aimed to compare activity and safety of three dual-nucleoside analogue reverse-transcriptase inhibitor (NRTI) regimens with or without a protease inhibitor in previously untreated children with HIV-1.

Methods In our multicentre trial, we randomly assigned 36 children to zidovudine and lamivudine, 45 to zidovudine and abacavir, and 47 to lamivudine and abacavir. Children who were symptomfree (n=55) were also randomly assigned to receive nelfinavir or placebo. Children with more advanced disease received open-label nelfinavir (73). Primary endpoints were change in plasma HIV-1 RNA at 24 and 48 weeks for the NRTI comparison and occurrence of serious adverse events for both randomised comparisons. Analyses were by intention to treat.

Findings Children had a median CD4 percentage of 22% (IQR 15–29) and a mean HIV-1 RNA concentration of 5·0 log copies/mL (SD 0·8). One child was lost to follow-up and one died of sepsis. At 48 weeks, in the zidovudine/lamivudine, zidovudine/abacavir, and lamivudine/abacavir groups, mean HIV-1 RNA had decreased by 1·71, 2·19, and 2·63 log copies/mL, respectively (estimated in absence of nelfinavir) (p=0·02 after adjustment for baseline factors). One child had a hypersensitivity reaction to abacavir; and three with possible reactions stopped abacavir. There were 24 serious adverse events—six in the symptom-free children (all on nelfinavir), but none were attributed to nelfinavir.

Interpretation Regimens containing abacavir were more effective than zidovudine/lamivudine. Such regimens could be combined with protease inhibitors and non-nucleoside reverse transcriptase inhibitors for safe and effective treatment of previously untreated children with HIV-1.

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Introduction

Combination antiretroviral treatment is the standard care for adults[1,2] and children[3,4] needing treatment for HIV-1 infection in well-resourced countries. However, therapeutic options for children are limited by unsuitable formulations and inadequate pharmacokinetic data for many drugs. Volume, taste, and dose frequency also need consideration, as does the ability of any combination to control the high concentrations of HIV-1 RNA in plasma that are seen in young children. Data for use of protease inhibitors in children were few when this trial began. The risks and benefits of these drugs as first-line treatment had not been defined in previously untreated children. Paediatric formulations of protease inhibitors, when available, were not accepted well by children. A powder formulation of nelfinavir has been developed with a recommended dose of 60–90 mg/kg daily for children aged older than 2 years.[5]

Abacavir is a new nucleoside-analogue reverse-transcriptase inhibitor (NRTI) with a liquid formulation.[6,7] Data for use of abacavir with lamivudine as a dual NRTI backbone in adults or children were few at the start of the study. However, because both drugs were available as small-volume, palatable, liquid formulations to be given twice daily without dietary restrictions, this combination was thought to be suitable for children. Although both drugs had been associated with development of the M184V mutation,[8,9] whether such an association would affect the efficacy of the drugs in combination was unknown. We aimed to assess the antiviral activity and safety of three dual NRTI treatment combinations and the safety and tolerability of the protease inhibitor nelfinavir in children with HIV-1 who had not previously been treated.

Methods

Participants

Children were eligible if they were aged 3 months to 16 years, had evidence of HIV-1 infection, and had received no antiretroviral treatment unless given as in-utero or perinatal prophylaxis up to 6 weeks after delivery. They were not eligible if they were receiving cytotoxic treatment for malignant disease or had haematological, hepatic, or renal contraindications to abacavir, zidovudine, lamivudine, or nelfinavir. The protocol was approved by the ethics committee for each participating centre. All primary caregivers gave written informed consent to participate, and additional written consent was obtained from children, where appropriate, according to their age and knowledge of HIV-1 status.

Trial design

PENTA 5 was a randomised, partly blinded (for nelfinavir) multicentre comparative trial. The trial consisted of two parts. In part A, we included children who were symptomfree, and in part B, enrolled those with more advanced disease. Paediatricians recruited children to either part A or B on the basis of their own assessment of clinical, virological, and immunological factors. All children were randomly assigned to one of three dual NRTI regimens: zidovudine (360 mg/m^2 per day taken twice or thrice daily)

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and lamivudine (8 mg/kg per day taken twice daily); zidovudine and abacavir (16 mg/kg per day taken twice daily); or lamivudine and abacavir. Children in part A were also randomly assigned to nelfinavir or matched nelfinavir placebo, available in powder or tablet form (75–90 mg/kg per day taken three times daily). All children in part B received open-label nelfinavir. Randomisation, which was done by the paediatrician faxing to one of two central trial offices in the UK and France to maintain treatment concealment, was stratified by country, and a minimisation algorithm was used to maintain balance between randomised groups for age and in-utero antiretroviral treatment received. Assignment to nelfinavir or placebo was the only masked part of the trial, and only the statisticians at the trial offices had access to group assignment.

Primary outcomes for the comparison between the three NRTI regimens (part A and B combined) were change in viral load from baseline to week 24 and 48, as measured by plasma HIV-1 RNA, and occurrence of serious adverse events. The latter was the primary outcome for the comparison of nelfinavir and placebo in part A. Serious clinical and laboratory events were those graded 3 or 4 according to common toxic effects criteria of the US National Cancer Institute that had been modified for children. Secondary outcomes were change in concentrations of HIV-1 RNA in plasma (part A), CD4 cell count and percentage, height, weight, and progression to AIDS, for comparison of the NRTI groups and of nelfinavir with placebo.

Procedures

Children were assessed at randomisation (week –2), at prescription of trial drugs (week 0), then at 2, 4, 8, 16, 20, 24 weeks, and every 8 weeks thereafter for a median of 59 weeks (IQR 49·5–72·0) to July 1, 2000. At each visit, we did a clinical assessment, and measured full blood count, biochemistry, concentrations of amylase in serum, concentration of HIV-1 RNA in plasma, and T-cell lymphocyte subsets. The data and safety monitoring committee met in January, 1998, September, 1998, January, 1999, and June, 1999 to review data that had not been masked. Guidelines for recommending modification of the trial included that, at an interim analysis, a difference of at least three SDs of a major endpoint was needed.[10]

T-cell lymphocyte subsets were measured by flow cytometry in every clinical centre. HIV-1 RNA concentration in plasma was measured at two central laboratories (Covance Central Laboratory Services, Geneva, for European centres, and Indianapolis, USA, for Brazil), which were accredited by the College of American Pathologists laboratory accreditation programme. We measured HIV-1 RNA concentration at weeks –2 and 0 using the Roche standard Amplicor assay version 1.5 (Roche Diagnostic Systems, USA), which had a limit of detection of 400 copies/mL; we tested subsequent samples with the Roche UltraSensitive assay version 1.5, which had a limit of detection of 50 copies/mL. Any sample with more than 40 000 copies/mL on the ultrasensitive assay was retested with the standard assay.

Statistical analysis

Efficacy was analysed on an intention-to-treat basis. Analyses of adverse events were censored 30 days after discontinuation of all trial drugs; incidence of first events was compared with standard log-rank methods. Concentrations of HIV-1 RNA in plasma were log transformed before analysis. Baseline values were those recorded nearest to, but before and within, 4 weeks of randomisation. The closest value to each scheduled visit week within equally spaced windows was used to calculate changes from baseline (with 4-week windows for assessment weeks 4, 8, 12, 16, 20, and 24, and 8-week windows subsequently). Where the concentration of HIV-1 RNA in plasma was below the lower limit of quantification (≤50 copies/mL), results were analysed by normal interval regression,[11] with these values replaced by the interval in which the true unobserved value could lie (ie, 0–50), rather than the limit of quantification.

We considered only randomised comparisons of zidovudine and lamivudine versus zidovudine and abacavir versus lamivudine and abacavir in all children (stratified by part A and part B), and nelfinavir versus placebo in part A. Because of minor differences in baseline characteristics and receipt of nelfinavir in the NRTI groups, analyses of the change in concentration of HIV-1 RNA in plasma were adjusted for age, HIV-1 RNA in plasma, and CD4 percentage at baseline; allocation to nelfinavir or placebo in part A or to part B (for the NRTI comparisons); and for NRTI group for comparison of nelfinavir with placebo. Thus, for NRTI comparisons, adjusted analyses compared the mean change in HIV-1 RNA in plasma in absence of nelfinavir for a child of 5 years with median baseline concentrations of HIV-1 RNA in plasma of 5·1 log copies/mL and CD4 percentage of 22% (the medians of these variables among all children). For comparison of nelfinavir with placebo in part A, adjusted estimates of mean change in log HIV-1 RNA in plasma assumed that a third of children were on each of the three NRTI combinations. Unadjusted comparisons of proportions were done with Fisher's exact tests, and adjusted analyses of proportions used logistic regression with Wald tests. CD4 cell counts, height, and weight were expressed as z scores with reference to healthy children who were not infected with HIV-1.[12,13] The study had 80% power to detect a difference of 0·5 log copies/mL in the change in HIV-1 RNA concentration in plasma from baseline to week 24 between the three NRTI groups with an overall F test at 5% two-tailed significance, assuming an SD of 0·7 log copies/mL.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or in the writing of the report. The sponsors provided trial drugs and funded the costs of drug distribution and plasma HIV-1 RNA tests. A representative was given the opportunity to comment on drafts of the report.

Results

130 children were randomised between January, 1998, and April, 1999. Two were excluded before starting trial drugs because one had an abnormal concentration of amino-transferases, and the other had parental consent withdrawn. 73 children were enrolled in part B and 55 in part A. 36 children received zidovudine and lamivudine, 45 zidovudine and abacavir, and 47 lamivudine and abacavir. In part A, 30 children were allocated to nelfinivir and 25 to placebo. Two children who were randomly allocated to nelfinavir were excluded from the comparison of nelfinavir versus placebo only because they were supplied in error with placebo for a short period of time (figure 1).

Children were enrolled from 34 centres in nine countries. Eight were from Belgium, 12 Brazil, one France, 15 Germany, four Ireland, 38 Italy, seven Portugal, three Spain, and 40 UK. 119 (93%) of 128 children had acquired HIV-1 from mother-to-child transmission, and nine were infected through contaminated blood or blood products. Only nine mothers had received antiretroviral

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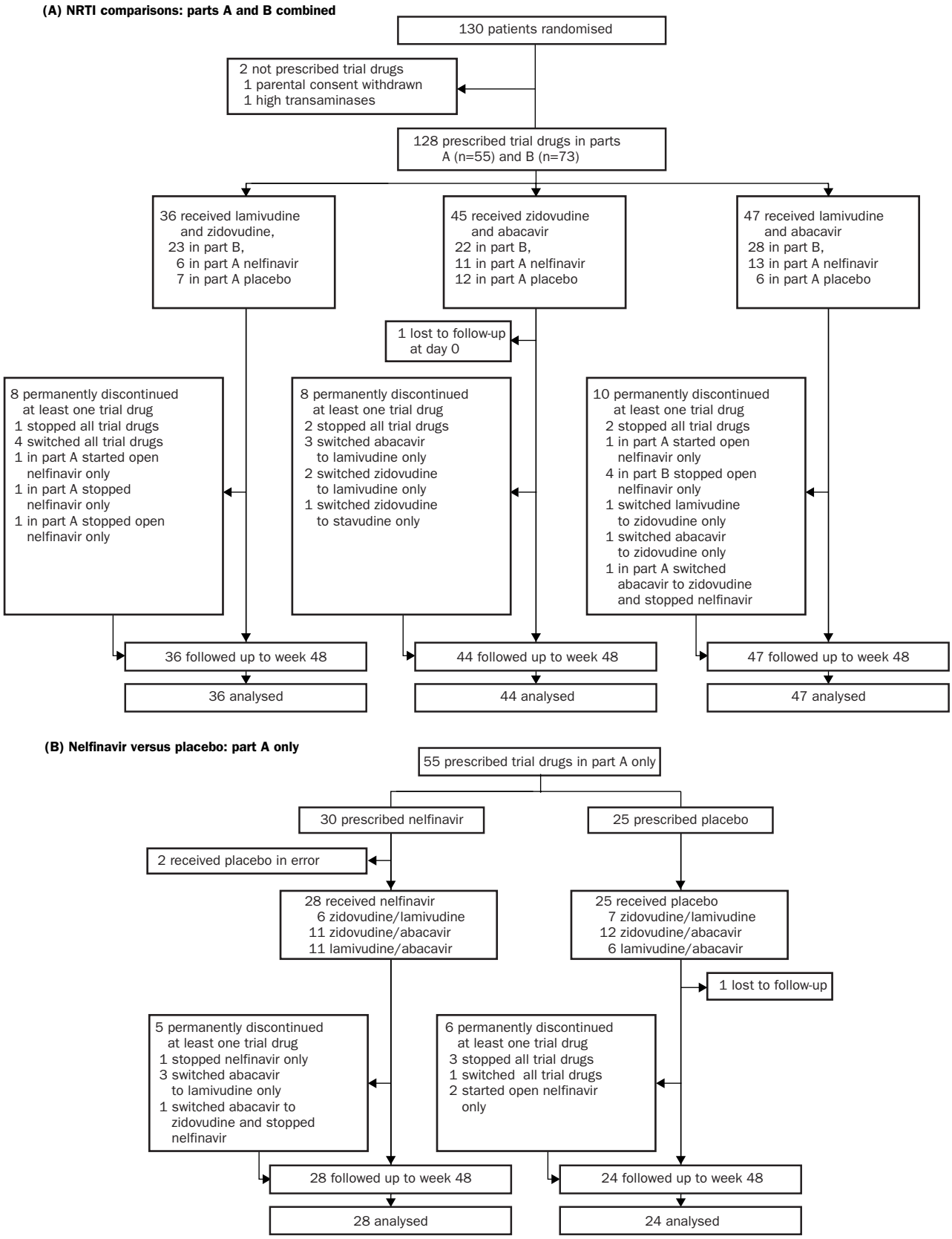

Figure 1: **Trial profile for parts A and B combined (A) and for part A only (B)**

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	Parts A and B combined			Part A	
	Zidovudine/lamivudine (n=36)	Zidovudine/abacavir (n=45)	Lamivudine/abacavir (n=47)	Nelfinavir (n=28)	Placebo (n=25)
Male sex	22 (61%)	25 (56%)	25 (53%)	21 (75%)	10 (40%)
Ethnic origin					
White	17 (47%)	24 (53%)	18 (38%)	17 (61%)	12 (48%)
Black	16 (44%)	18 (40%)	20 (43%)	10 (36%)	9 (36%)
Other	3 (8%)	3 (7%)	9 (19%)	1 (3%)	4 (16%)
Age (years)					
<2	7 (19%)	6 (13%)	12 (26%)	3 (11%)	2 (8%)
2–5	13 (36%)	11 (24%)	11 (23%)	10 (36%)	4 (16%)
>5	16 (44%)	28 (62%)	24 (51%)	15 (54%)	19 (76%)
Median (range)	4·5 (0·3 to 12·4)	6·1 (0·4 to 15·5)	5·2 (0·3 to 16·7)	5·3 (1·1 to 12·7)	6·9 (0·5 to 15·5)
CDC disease stage[28]					
None	8 (22%)	13 (29%)	9 (19%)	8 (29%)	5 (20%)
A	9 (25%)	12 (27%)	12 (26%)	9 (32%)	9 (36%)
B	18 (50%)	14 (31%)	21 (45%)	11 (39%)	9 (36%)
C	1 (3%)	6 (13%)	5 (11%)	0	2 (8%)
In-utero zidovudine	3 (8%)	3 (7%)	3 (6%)	1 (4%)	2 (8%)
Plasma HIV-1 RNA (mean [SD]; log_{10} copies/mL)	5·03 (0·82)	4·89 (0·72)	5·13 (0·75)	4·72 (0·70)	4·49 (0·68)
CD4					
Count (median [IQR], cells/mL)	496 (346 to 904)	530 (340 to 1019)	602 (323 to 1063)	913 (434 to 1150)	539 (369 to 760)
Percentage (median, IQR)	18 (12 to 27)	22 (13 to 29)	22 (14 to 33)	26 (18 to 30)	23 (17 to 27)
Z score (median, IQR)	–2·8 (–4·1 to –1·5)	–2·5 (–4·3 to –0·9)	–2·8 (–4·3 to –0·5)	–1·5 (–3·3 to –0·3)	–2·6 (–4·0 to –1·5)
Z scores					
Height-for-age (median, IQR)	–0·91 (–1·83 to –0·04)	–0·76 (–1·38 to –0·21)	–1·05 (–1·82 to –0·35)	–1·32 (–1·67 to 0·57)	–0·71 (–1·32 to 0·01)
Weight-for-age (median, IQR)	–0·88 (–1·45 to 0·40)	–0·10 (–0·97 to 0·23)	–0·75 (–1·42 to 0·07)	–0·96 (–1·27 to 0·24)	–0·24 (–1·08 to 0·25)

Table 1: **Baseline demographics and laboratory measurements**

treatment during pregnancy (all had zidovudine), reflecting the fact that many of the children had been born abroad or had mothers who had not been diagnosed with HIV-1 during pregnancy. Seven (78%) of these children also received zidovudine perinatally (five for 6 weeks, one for 7 weeks, and one for 13 weeks (a minor protocol violation randomised to lamivudine and abacavir). Median age at entry to the trial was 5·3 years (range 0·3–16·7), and 26 (20%) children were younger than 2 years. CD4 cell count and percentage were higher, and concentration of HIV-1 RNA in plasma lower in children in part A than in those in part B. Demographic and disease characteristics were much the same in the three dual NRTI groups and in the nelfinavir and placebo groups in part A (table 1).

One child was lost to follow-up (after 3 days) and one died in the first month after starting treatment (part B, allocated to lamivudine/abacavir); all other children were followed up to at least week 48 (figure 1). Median follow-up to July 1, 2000, was 59·2 weeks (range 0·4–87·9). 85%, 84%, and 86% of total time to week 48 was spent on prescribed NRTI treatment as allocated in the zidovudine/lamivudine, zidovudine/abacavir, and lamivudine/abacavir groups, respectively; and 84% and 79% on prescribed nelfinavir and placebo in part A. Remaining time not spent on randomised treatment was because of interruptions or changes to treatment due to adverse events, poor RNA response, or parental request (according to protocol).

35 children started nelfinavir/placebo powder, of whom 13 (37%) were younger than 2 years. 27 (77%) switched to tablets (18 in the first 8 weeks). In December, 1998, data became available suggesting that a higher dose of nelfinavir was needed in children, and that twice daily dosing was as effective as thrice daily.[14] The protocol dose of nelfinavir was thus increased to a minimum of 90–110 mg/kg daily, with twice daily dosing allowed. Ten (8%) children started nelfinavir/placebo twice daily; 43 switched

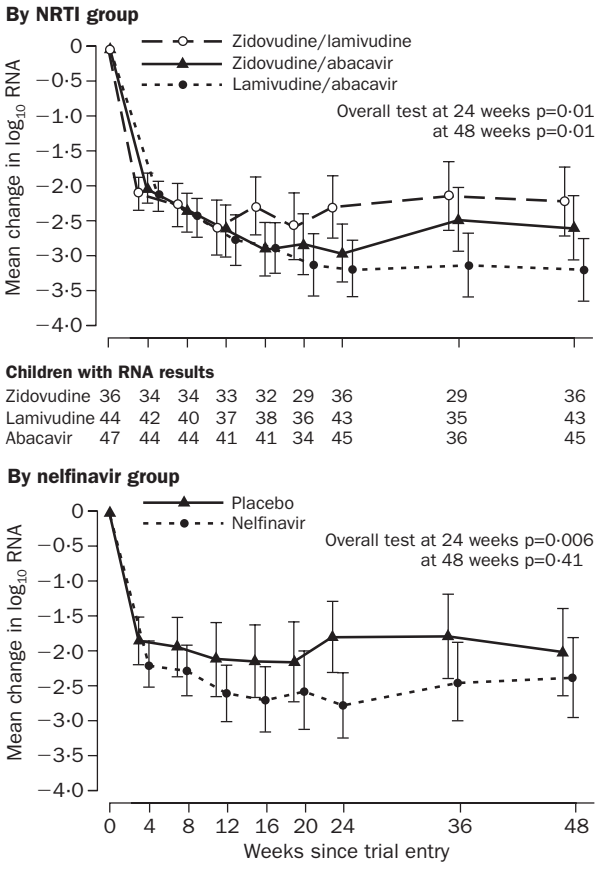

Figure 2: **Change in concentration of log_{10} HIV-1 RNA in plasma from trial entry to week 48 (unadjusted)**

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	Zidovudine/lamivudine (1) (n=36)	Zidovudine/abacavir (2) (n=43)*	Lamivudine/abacavir (3) (n=45)*	(1) vs (2) Adjusted p	(1) vs (3) Adjusted p	(2) vs (3) Adjusted p	Adjusted overall p
Week							
24	–1·34 (0·31)	–2·09 (0·30)	–2·11 (0·31)	0·007	0·006	0·93	0·008
48	–1·71 (0·36)	–2·19 (0·35)	–2·63 (0·37)	0·14	0·005	0·16	0·02

Values are mean (SE). *Data missing from two patients.

Table 2: **Change in concentration of HIV-1 RNA in plasma estimated for a child with median age, baseline CD4 percentage and HIV-1 RNA in absence of nelfinavir**

from thrice to twice daily schedules during the trial.

An unadjusted comparison showed significant differences between NRTI groups in the change in HIV-1 RNA from baseline at 24 and 48 weeks (overall p=0·01 and p=0·01, respectively), and for nelfinavir/placebo groups at 24 but not 48 weeks (overall p=0·006 and p=0·41, respectively; figure 2). The NRTI effects did not differ significantly between parts A and B (heterogeneity test p=0·38 at 24 weeks, p=0·59 at 48 weeks).

After correction for minor differences in baseline characteristics and receipt of nelfinavir, the adjusted analysis showed similar results for change in HIV-1 RNA between the NRTI groups at 24 and 48 weeks (table 2). Most of the difference was accounted for by larger reductions in plasma HIV-1 RNA in the regimens containing abacavir than in the zidovudine/lamivudine group at week 24. The difference between zidovudine/abacavir and zidovudine/lamivudine was 0·75 log copies/mL (95% CI 0·20–1·29), and between lamivudine/abacavir and zidovudine/lamivudine 0·77 log copies/mL (0·22–1·32). At week 48, most of the difference was accounted for by the reduction in the lamivudine/abacavir group than in the zidovudine/lamivudine group (difference 0·92 log copies/mL [0·28–1·55]). Analyses of the proportions of children with concentrations of HIV-1 RNA in plasma that were 400 copies/mL or less and 50 copies/mL or less showed similar results (table 3).

Overall, 24 serious adverse events occurred in 18 children. Of these, four were clinical events: one death (lamivudine/abacavir/nelfinavir, part B), one hypersensitivity reaction to abacavir (zidovudine/abacavir/nelfinavir, part A), one stroke (subsequently confirmed to be due to HIV-1 encephalopathy, lamivudine/abacavir/nelfinavir, part B), and one vomiting (zidovudine/abacavir/nelfinavir, part A). Of the 20 laboratory grade 3 or 4 events, most frequent were neutropenia (12 episodes) and thrombocytopenia (three episodes). Three children in each of the NRTI groups had one or more episodes of neutropenia. Only two serious adverse events resulted in permanent discontinuation of one or more drugs (the child who died had stopped all drugs before death, and the child with hypersensitivity stopped abacavir and changed to lamivudine). No differences were recorded between the three NRTI groups in the time to first serious adverse event (log-rank p=0·51). Four children in part A had six serious adverse events (six nelfinavir, zero placebo, log-rank p=0·06), all of which were attributed to NRTI drugs, and none led to permanent discontinuation of nelfinavir.

Six children permanently stopped drugs after minor adverse events: vomiting (two nelfinavir, one zidovudine); cutaneous reaction (one lamivudine); fever assumed to be early hypersensitivity (one abacavir); and anaemia (one zidovudine). Two other children stopped abacavir permanently because of hypersensitivity reactions thought to be associated with abacavir, but subsequently judged to be due to otitis media and a respiratory infection, respectively. Of 91 children starting abacavir, eight (9%) stopped abacavir permanently because of two serious adverse events (one death, one hypersensitivity), one minor adverse event, two other illnesses (above), two parent or child requests, and one non-compliance. 12 (13%) children had 15 recorded interruptions of abacavir, lasting a median of 6 days (range 1–85) followed by restarting the drug; no child had a hypersensitivity reaction on restarting abacavir.

In part A, incidence of minor adverse events per 100 child-years was similar in the nelfinavir and placebo groups (84·8 for nelfinavir, 84·4 for placebo; p=0·26). However, all 13 diarrhoea events (six children, incidence 17·6 per 100 child-years) occurred in the nelfinavir group (p=0·01); none resulted in discontinuation of trial drug. Two of the six children who stopped trial drug after minor adverse events were in part A (one vomiting [nelfinavir], one fever [abacavir]).

In a post-hoc analysis, fasting lipid data were available for 32 children in part A and 41 in part B on at least one occasion, with the closest measurement to week 48 at a median of 43 weeks (range 18–81) from trial entry. For children in part A, median total cholesterol concentration was 4·14 mmol/L (2·9–5·6) in the nelfinavir group, compared with 4·04 mmol/L (2·6–5·3) in the placebo group; one child (placebo) had grade 1 hypercholesterolaemia. Median triglyceride concentrations were 0·92 mmol/L (0·56–1·35) and 1·00 mmol/L (0·36–1·90) in the nelfinavir and placebo groups, respectively; one child had grade 1 triglyceridaemia (placebo). No child had grade 3 or 4 cholesterol or triglyceride concentrations, and no child developed clinical lipodystrophy.

Adjusting for age, baseline HIV-1 RNA, CD4 percentage, and on the assumption that a third of the children were in each NRTI group, mean decrease in HIV-1 RNA in plasma at week 24 was 0·79 log copies/mL (95% CI 0·18–1·41) greater in the nelfinavir than in the placebo group, but at week 48, the difference was only 0·14 log copies/mL (–0·91 to 0·63) (table 4). The proportion of children with HIV-1 RNA of 50 log copies/mL or less was

	Zidovudine/ lamivudine (1) (n=36)	Zidovudine/ abacavir (2) (n=43)*	Lamivudine/ abacavir (3) (n=45)*	(1) *vs* (2) exact p	(1) *vs* (3) exact p	(2) *vs* (3) exact p	Overall exact p	Adjusted p†
Week								
24								
<50 copies/mL	14 (39%)	21 (49%)	22 (49%)	0·50	0·50	1·00	0·62	0·65
<400 copies/mL	16 (44%)	32 (74%)	34 (76%)	0·01	0·006	1·00	0·006	0·006
48								
<50 copies/mL	11 (31%)	19 (44%)	25 (56%)	0·25	0·03	0·39	0·09	0·10
<400 copies/mL	16 (44%)	26 (60%)	32 (71%)	0·18	0·02	0·37	0·05	0·05

Values are number (%). *Data missing for two patients. †Adjusted for receipt of nelfinavir in part A and B, age, baseline CD4 percentage, and plasma HIV-1 RNA by logistic regression.

Table 3: **Children with low concentrations of HIV-1 RNA in plasma below 50 and 400 copies/mL**

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	Placebo (n=23)*	Nelfinavir (n=28)†	Adjusted p
Week			
24	–1·81 (0·25)	–2·60 (0·22)	0·01
48	–2·20 (0·32)	–2·33 (0·29)	0·73

Values are mean (SE). *Data missing for one patient at 24 and 48 weeks. †Data missing for one patient at 48 weeks only.

Table 4: **Change in concentration of HIV-1 RNA in plasma adjusted for age, baseline CD4 percentage, and HIV-1 RNA, and for NRTI group**

significantly greater in the nelfinavir group at 24 weeks (p=0·04), but not at week 48 (table 5).

Three (3%) children (one nelfinavir, one placebo [part A] and one in part B) of 116 children with no AIDS diagnosis at entry developed an AIDS-defining illness (one in each NRTI group), and one child with AIDS at trial entry (part B, zidovudine/abacavir/nelfinavir) had a second AIDS event. One child in part B, who had encephalopathy and sepsis at trial entry, died. After acute onset of fever, the child collapsed and had a cardiac arrest 9 days into treatment with lamivudine/abacavir/nelfinavir. The executive committee and the data and safety monitoring committee reviewed the case and judged that sepsis was the most probable cause of death, although this diagnosis was not proven. The possibility of a reaction to abacavir cannot be completely excluded because the child was never rechallenged. However, such a reaction was deemed unlikely because of rapid onset of symptoms, absence of a rash or raised aminotransferase concentrations, and previous history of sepsis in a child with an AIDS diagnosis at trial entry. The child did not have a necropsy.

The change in height-for-age z score at 24 and 48 weeks differed significantly between the three dual NRTI groups (table 6). However, median increases in weight-for-age z score, CD4 cell count, CD4 percentage, and CD4 z score did not differ between these groups (table 6), nor between the nelfinavir and placebo groups in part A (data not shown).

	Placebo (n=23)*	Nelfinavir (n=28)†	Exact p	Adjusted p‡
Week				
24				
<50	6 (26%)	16 (57%)	0·05	0·03
<400	12 (52%)	19 (68%)	0·39	0·21
48				
<50	8 (35%)	13 (48%)	0·40	0·30
<400	12 (52%)	15 (56%)	1·00	0·99

Values are number (%). *Data missing for one patient at 24 and 48 weeks. †Data missing for one patient at 48 weeks only. ‡Adjusted for median age, baseline CD4 percentage, HIV-1 RNA in plasma, and NRTI group by logistic regression.

Table 5: **Children with concentrations of HIV-1 RNA in plasma below 50 copies/mL and 400 copies/mL**

Discussion

In Europe and the USA, successful interventions to reduce mother-to-child transmission of HIV-1 have resulted in a sharp decrease in the number of children born with HIV-1 infection, and few infected children in these countries remain untreated. PENTA 5 assessed highly active antiretroviral treatment in children who have not previously been treated, and was designed to address more than one question. By chance, the number of children allocated to the NRTI groups differed; some differences in baseline characteristics were also recorded. Therefore, our primary analyses adjusted for baseline factors and estimated results in the absence of nelfinavir for comparison of the NRTI groups, and on the assumption that a third of children were on each of the NRTI groups for the nelfinavir/placebo comparison. Unadjusted analyses gave similar results.

Of 119 children infected by mother-to-child transmission, only nine mothers had received zidovudine during pregnancy. However, in a resistance substudy[15] of 113 children enrolled in PENTA 5, no child had primary mutations in either reverse transcriptase or protease, and we saw no genotypic resistance to any antiretroviral drug according to the virtual phenotype at trial entry (VircoGEN, VIRCO, Belgium).

Results of two trials[6,16] of abacavir in combination with other NRTIs in children with HIV-1 who had received previous treatment have shown that the safety profile of abacavir was close to that seen in adults. However, differences in laboratory markers of activity between the zidovudine/lamivudine/abacavir and zidovudine/lamivudine groups were small but difficult to interpret because children had received extensive previous NRTI treatment, especially with zidovudine and lamivudine.[16] Results of the PENTA 5 trial have shown that abacavir-containing NRTI regimens are more effective than zidovudine/lamivudine, which is one of the standard NRTI combinations recommended for children starting triple antiretroviral treatment. Of the dual NRTI regimens compared, abacavir/lamivudine resulted in the largest and most durable reduction in viral load, after controlling for baseline factors and use of nelfinavir. The change in height-for-age z score paralleled the changes in HIV RNA in the three dual-NRTI regimens. Such an association has been reported in trials[17] that compared monotherapy with dual treatment, and suggests that growth could be directly affected by presence of HIV-1. Growth could be a useful surrogate marker for assessing the efficacy of antiretroviral regimens.

At the time PENTA 5 was started, we were concerned that the combination of lamivudine and abacavir might not provide a potent or sustainable reduction in concentrations of HIV-1 RNA in plasma, since both drugs were associated

	Zidovudine/lamivudine (n=36)	Zidovudine/abacavir (n=45)	Lamivudine/abacavir (n=47)	Overall p*
Measurements				
CD4 percentage				
24 weeks	7 (4 to 10)	7 (5 to 9)	7 (5 to 9)	0·94
48 weeks	9 (7 to 11)	9 (7 to 11)	9 (7 to 11)	0·80
CD4 count (absolute, cells/mL)				
24 weeks	223 (133 to 314)	162 (181 to 243)	217 (138 to 296)	0·79
48 weeks	182 (2 to 361)	218 (57 to 379)	272 (111 to 434)	0·97
CD4 z score				
24 weeks	1·20 (0·79 to 1·61)	1·08 (0·71 to 1·45)	1·48 (1·12 to 1·84)	0·77
48 weeks	1·00 (0·24 to 1·75)	1·21 (0·54 to 1·89)	1·58 (0·90 to 2·25)	0·75
Height-for-age z score				
24 weeks	–0·01 (–0·17 to 0·15)	0·10 (–0·04 to 0·25)	0·13 (–0·02 to 0·27)	0·02
48 weeks	0·03 (–0·16 to 0·21)	0·10 (–0·07 to 0·27)	0·29 (0·12 to 0·47)	0·0007
Weight-for-age z score				
24 weeks	0·10 (–0·07 to 0·26)	0·05 (–0·10 to 0·20)	0·14 (–0·01 to 0·28)	0·16
48 weeks	0·15 (–0·03 to 0·33)	–0·03 (–0·19 to 0·14)	0·17 (0·00 to 0·34)	0·09

Values are median (95% CI). *p value calculated with Kruskal-Wallis test.

Table 6: **Change from baseline in CD4 cell count, CD4 percentage, CD4 z score, height for age, and weight for age by NRTI group**

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with development of the M184V mutation. However, subsequent studies[8,9,18] have shown that M184V alone, although giving high-level phenotypic resistance to lamivudine, does not diminish the response to abacavir compared with wild-type virus. The results of our PENTA 5 trial[15] showed that phenotypic resistance to abacavir only arose if M184V was present with one or more of L74V, K65R, or Y115F mutations. Adherence to medication is important to achieve and sustain concentrations of HIV-1 RNA in plasma below the limit of assay quantification.[19] Lamivudine and abacavir are available as tolerable-tasting liquids, which can be given twice daily in identical small volumes, with or without food. Good adherence could have contributed to the effectiveness of this combination in PENTA 5.

A hypersensitivity reaction to abacavir takes place in 3–5% of adults in clinical trials, and can be especially severe if individuals are rechallenged. In PENTA 5, four children (3%) stopped abacavir because of a possible reaction. In two of these children, the symptoms were subsequently attributed to acute infections, emphasising the difficulties in distinguishing hypersensitivity reactions from acute infections. Abacavir should be stopped if clinical presentation is consistent with a reaction, irrespective of the probability of an infectious cause. The other two possible reactions were in the first month of treatment, as in previous reports in adults and children.[7,16,18,20,21] A hypersensitivity reaction to abacavir was judged very unlikely in the child who died but cannot be ruled out because no rechallenge took place. Of 557 children (not including those in PENTA 5) who have received abacavir in trials and in compassionate release programmes, no deaths have been deemed to be due to abacavir.[6,7,16] On the basis of seven reports in adults, none of whom were enrolled in a clinical trial, concern has been expressed that hypersensitivity reactions could arise from restarting abacavir after interruption of treatment, even in the absence of any symptoms of a hypersensitivity reaction before stopping.[22] In an analysis of over 1000 adults enrolled in abacavir trials, no reactions were seen among the 16% of these patients who stopped and restarted abacavir (Dr Gill Pearce, GlaxoSmithKline, personal communication). In this trial, we recorded no hypersensitivity reactions in children who stopped abacavir once or twice for up to 85 days and then restarted.

Although nelfinavir tablets were well tolerated in this trial, the powder was not. The large volume of powder, unpleasant consistency, and difficulties in dissolving the powder in milk or food resulted in most children quickly switching to tablets, which can be crumbled in a small volume of water, and added to milk or food. Adverse events attributed to nelfinavir were infrequent except for diarrhoea, which was mild even with high doses. We recorded no clinical lipodystrophy, and the difference in fasting lipids between nelfinavir and placebo groups, was small (although based on few data). Longer follow-up of large numbers is needed to better define changes in lipid metabolism due to antiretroviral treatment and its long-term clinical effects on children.

The change in plasma HIV-1 RNA from baseline at week 24 was nearly 0·8 log copies/mL greater in the nelfinavir group than the placebo group at 24 weeks, and significantly more children on nelfinavir had HIV RNA values of less than 50 copies/mL. However, at 48 weeks, the difference between the two groups was only 0·14 log copies/mL, even though most children remained on their allocated treatment. Most children started the trial on nelfinavir doses between 60 and 90 mg/kg daily, although the dose was increased to a minimum of 90 mg/kg daily during the trial. New pharmacokinetic data have suggested that 90 mg/kg nelfinavir daily is a better dose for children,[14] and that higher doses might also be required in adults.[23] Data for very young infants have shown that even with daily nelfinavir doses of 150 mg/kg, attaining adequate pharmacokinetic data profiles is difficult.[24] In some children in our trial, suboptimum nelfinavir dose associated with development of resistance to nelfinavir or other trial drugs, could explain some of the difference in antiviral effect attributable to nelfinavir at 24 and 48 weeks.

Trials of HIV-1 infection in children are few, and in most trials of highly active antiretroviral treatment, children have received previous NRTI treatment. Thus, prediction of the proportion of children who are likely to achieve viral suppression on their first antiretroviral regimen is difficult, especially because of the extremely high viral loads in some children. Results of the PACTG 338[25] and 377[14] trials showed that 40–50% of children receiving two NRTIs and ritonavir or nelfinavir had less than 400 copies HIV-1 RNA/mL at 24 weeks, compared with an average of 64% in PENTA 5, in which 20% of children were only on two NRTIs. Previous NRTI treatment could account for lower response rates, since children had higher CD4 percentage and lower HIV RNA at baseline in both of these trials than in PENTA 5. In a third study[26] of children who had previously been given NRTIs, and who had a median HIV RNA of 10 000 copies/mL at baseline, nelfinavir and efavirenz were combined with an NRTI; at 48 weeks, the proportion with concentrations of HIV-1 RNA in plasma of less than 400 copies/mL was 76%, and 63% had less than 50 copies/mL. Data from an open-label study[27] of a new protease inhibitor, lopinavir/ritonavir, in combination with two NRTI have been presented showing that in an intention-to-treat analysis, the proportion with HIV RNA of less than 400 copies/mL by 48 weeks was 84% in children who had not had previous treatment (n=44), 88% in those who had had NRTI previously (32), and 58% in those who had previously had both NRTI and protease inhibitors (24).

Results of our PENTA 5 trial have shown that of the dual NRTI regimens compared, abacavir-containing regimens are more effective than zidovudine/lamivudine in children with HIV-1 who have not previously been treated. These combinations could provide a good NRTI backbone for use with protease inhibitors and non-nucleoside reverse-transcriptase inhibitors. Because children have fewer treatment options than do adults, a potent first-line antiretroviral treatment regimen that is also well tolerated is urgently needed. Our results with abacavir in this trial suggest that the saftety profile in children is similar to that in adults.

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Conflict of interest statement

None declared.

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References

1 Harindra V. British HIV Association guidelines for antiretroviral treatment of HIV seropositive individuals. *Lancet* 1997; **349:** 1086–92.

2 Carpenter CCJ, Fischl MA, Hamner SM, et al. Antiretroviral therapy for HIV infection in 1997. Updated recommendations of the International AIDS Society-USA Panel. *JAMA* 1997; **277:** 1962–69.

3 Centers for Disease Control and Prevention. Guidelines for the use of antiretroviral agents in pediatric HIV infection. *MMWR Morb Mortal Wkly Rep* 1998; **47:** 1–43.

4 Sharland M, Gibb DM, Giaquinto C. Current evidence for the use of paediatric antiretroviral therapy—a PENTA analysis. *Eur J Paediatr* 2000; **159:** 649–56.

5 Krogstad P, Wiznia A, Luzuriaga K, et al. Treatment of human immunodeficiency virus 1-infected children with the protease inhibitor nelfinavir mesylate. *Clin Infect Dis* 1999; **28:** 1109–18.

6 Hughes W, McDowell JA, Shenep J, et al. Safety and single-dose pharmacokinetics of abacavir (1592U89) in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother* 1999; **43:** 609–15.

7 Kline MW, Blanchard S, Fletcher CV, et al. A phase I study of abacavir (1592U89) alone and in combination with other antiretroviral agents in infants and children with human immunodeficiency virus infection. *Pediatrics* 1999; **103:** E471–75.

8 Miller V, Sturmer M, Staszewski S, et al. The M184V mutation in HIV-1 reverse transcriptase (RT) conferring lamivudine resistance does not result in broad cross-resistance to nucleoside analogue RT Inhibitors. *AIDS* 1998; **12:** 705–12.

9 Tisdale, M, Alnadaf, T, Cousens D, et al. Combination of mutations in HIV-1 reverse transcriptase required for resistance to carbocyclic nucleoside 1592U89. *Antimicrob Agents Chemother* 1997; **41:** 1094–98.

10 Peto R, Pike MC, Armitage P, et al. Design and analysis of randomised clinical trials requiring prolonged observation of each participant, II: analysis and examples. *Br J Cancer* 1977; **35:** 1–39.

11 Arnemyia T. Regression analysis when the dependent variable is truncated normal. *Econometrica* 1973; **41:** 997–1016.

12 Wade AM, Ades AE. Age related reference ranges: significance test for models and confidence intervals for centiles. *Stat Med* 1994; **13:** 2359–67.

13 Freeman JV, Cole TJ, Chinn S, Jones PRM, White EM, Preece MA. Cross-sectional stature and weight reference curves for the UK 1990. *Arch Dis Child* 1995, **73:** 17–24.

14 Wiznia A, Stanley K, Krogstad P, et al. Combination nucleoside analog reverse transcriptase inhibitor(s) plus nevirapine, nelfinavir, or ritonavir in stable antiretroviral therapy-experienced HIV-infected children: week 24 results of a randomized controlled trial- PACTG-377. *AIDS Res Hum Retroviruses* 2000; **16:** 1113–21.

15 Kaye S, on behalf of the PENTA virology committee. Drug resistance in a trial of nucleoside-analogue and protease inhibitor therapy in children (PENTA 5). Fifth International Congress on Drug Therapy in HIV Infection. *AIDS* 2000; **14** (suppl)**:** 354.

16 Saez-Llorens, Nelson RP, Emmanuel P, and the CNAA3006 Study Team. A randomized double-blind study of triple nucleoside therapy of abacavir, lamivudine and zidovudine in previously treated human immunodeficiency virus type-1 infected children. *Pediatrics* 2001; **107:** U25–U35.

17 Paediatric European Network for Treatment of AIDS (PENTA). A randomised double-blind trial of the addition of lamivudine or matching placebo to current nucleoside analogue reverse transcriptase inhibitor therapy in HIV-infected children: the PENTA-4 trial. *AIDS* 1998; **12:** F151–60.

18 Katlama C, Clotet B, Plettenberg A, et al. The role of abacavir (ABC, 1592) in antiretroviral therapy-experienced patients: results from a randomized, double-blind trial. *AIDS* 2000; **14:** 781–89.

19 Watson DC, Farley JJ. Efficacy of and adherence to highly active antiretroviral therapy in children infected with human immunodeficiency virus type I. *Pediatr Infect Dis* 1999; **18:** 682–89.

20 Saag M, Sonnerborg A, Torres RA, et al, and the Abacavir Phase 2 clinical team. Antiretroviral effect and safety of abacavir alone and in combination with zidovudine in HIV-infected adults. *AIDS* 1998: **12:** 203–09.

21 Youle M for the CNA30017 study team. A novel use for abacavir to simplify therapy and reduce long-term toxicity in PI-experienced patients successfully treated with HAART: 48-week results. (Fifth International Congress on Drug Therapy in HIV Infection). *AIDS* 2000; **14** (suppl)**:** PL 6·4.

22 Important Safety information on hypersensitivity reactions and Ziagen (Abacavir sulfate). Letter to healthcare providers from Glaxo-Wellcome. August 2000.

23 Burger DM, Hugen RE, Aanouste RE, Hoetelmans RMW, on behalf of the ATHENA Study Group. Treatment failure of nelfinavir-containing triple therapy can largely be explained by low nelfinavir plasma concentrations. Fifth International Congress on Drug Therapy in HIV Infection. *AIDS* 2000; **14** (suppl)**:** P258.

24 Litalien C, Giaquinto C, Faye A, Mechinaud F, Grosch I. Nelfinavir doses should be increased in infants (The PENTA 7 Study). XIII International AIDS Conference 2000; Abstract MoPeB2213.

25 Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children. *JAMA* 2000, **283:** 492–98.

26 Starr SE, Fletcher Courtney V, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. *N Engl J Med* 1999; **341:** 1874–81.

27 Saez-Llorens X, Renz C, Deetz C, et al. Kaletra lopinavir /ritonavir in HIV-infected children at 48 weeks. Eighth Conference on Retroviruses and Opportunistic Infections (Chicago, February 2001), Abstract 680).

28 Centres for Disease Control. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR Morb Mortal Wkly Rep* 1994; **43:** 1–10.

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