Five year follow up of vertically HIV infected children in a randomised double blind controlled trial of immediate versus deferred zidovudine: the PENTA 1 trial

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Paediatric European Network for Treatment of AIDS (PENTA)

Abstract

A total of 195 children were randomised to zidovudine (immediate) or matching placebo (deferred) in a multicentre double blind trial in vertically HIV infected children with early disease (the PENTA 1 trial). Median follow up in the blinded phase was 1.9 years. Thereafter, individual children were unblinded following the results of adult trials showing a benefit of combination antiretroviral therapy (ART) over monotherapy, but follow up continued and is reported here until December 1998 (total follow up 4.6 years). Median time to starting ART in the deferred group was 2.7 years; 19% of deferred children had not started ART by 1999. Throughout follow up, the percentage of time spent on no ART, monotherapy, dual, and triple ART was 21%, 44%, 29%, and 6% respectively for immediate and 62%, 12%, 18%, and 8% for deferred groups. During the blinded phase eight (7.8%) immediate and 12 (13.3%) deferred children developed AIDS or died (log rank p = 0.24); overall 21 immediate and 20 deferred children progressed. In an analysis including all children regardless of original allocation, the risk of progression to AIDS or death, adjusting for age and time since trial entry was significantly lower during 1997–98 (2.4 per 100 child years) than during 1992–96 (6.6 per 100 child years), most likely a result of increased use of combination ART.

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Keywords: AIDS; HIV; zidovudine; PENTA; randomised; placebo-controlled

Paediatric European Network for Treatment of AIDS (PENTA)

See Appendix and website for committees and collaborators

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Zidovudine (ZDV) monotherapy was the first antiretroviral therapy (ART) shown to be effective in the treatment of HIV infection. In the first trial, ZDV significantly delayed disease progression and death in adults with AIDS or advanced AIDS related complex over an average of 16 weeks.[1] Subsequently, trials in adults with asymptomatic infection reported short term benefits from ZDV alone, but no improvement in survival.[2–5] In the early 1990s, data from cohort studies and hospital based case series of perinatally infected children suggested that progression to AIDS and death was faster in children compared with adults and that the natural history in children differed from adults in several important respects.[6–8] Small uncontrolled studies suggested that ZDV improved clinical status, particularly in children with HIV encephalopathy.[9] It was argued that results from adult trials, for example those investigating the timing of commencement of ZDV, could not always be extrapolated to children. There were considerable differences in the timing of initiation of ZDV therapy between paediatric centres in Europe. Therefore the PENTA (Paediatric Network for Treatment of AIDS) 1 trial was started, but was terminated when benefits of combination therapy over ZDV monotherapy were shown in adults. We describe disease progression in children with mild or no HIV related symptoms who were originally randomised to immediate (IMM) or deferred (DEF) ZDV in the PENTA 1 trial.

Participants and methods

PARTICIPANTS

Children aged 3 months to 16 years with vertically acquired HIV infection were eligible if they had not developed AIDS (CDC classification group C[10]), had received no previous ART, and the paediatrician was unsure whether to commence ZDV immediately or defer until symptoms developed. The relevant ethics committee for each participating centre approved the protocol. All parents/care givers and children, where appropriate, gave written consent.

TRIAL DESIGN

PENTA 1 was a randomised double blind placebo controlled trial. The planned intake was 400 children with three years follow up. Children were randomly allocated in a 1:1 ratio to receive ZDV 600 mg/m^2 syrup (10 mg/ml) per day in three divided doses (immediate, IMM) or matching placebo (deferred, DEF). Randomisation was stratified by clinical centre and country and was undertaken centrally by trials centres in London (for the UK, Germany, Netherlands, Canada, Sweden, Ireland, Italy, and Brazil) and Paris (for France, Belgium, Spain, and Switzerland).

All children who developed AIDS were to be offered open label ZDV. In addition, children developing non-AIDS clinical progression or rapidly falling CD4+ cell counts could receive open label ZDV according to predefined clinical guidelines. Where possible the paediatrician and parents remained blind to the original randomisation. All children were to be followed to

the end of the trial or until they died. Concomitant medication was allowed, including prophylaxis for *Pneumocystis carinii* pneumonia.

TRIAL MANAGEMENT

Recruitment started in September 1992. In March 1995, following results of the PACTG 128 trial showing no difference in efficacy (but increased toxicity) with 720 mg versus 360 mg/m^2/day of ZDV,[11] children could receive ZDV/placebo at a dose of between 360 and 600 mg/m^2/day. In October 1995, after results of trials in previously untreated adults showed a significant clinical benefit from the combination of two nucleoside analogue reverse transcriptor inhibitor (NRTI) drugs compared with ZDV monotherapy,[12 13] the blinded phase was discontinued and individual children and parents were told their original treatment allocation. Those already on ZDV (IMM) could add a second drug, and those in the DEF group could commence combination therapy when they required treatment. The trial results were not unblinded and follow up of all children continued, participants being encouraged to continue the original randomised policy of either immediate or deferred ART on an open basis. Data until the end of December 1998 are reported here.

The Data and Safety Monitoring Committee reviewed the unblinded data 6–9 monthly to October 1995, and yearly during the open phase of the trial. All data on eligibility, baseline characteristics, adverse events, and AIDS events or death, and 10% of all other data were validated against original clinic records. An independent committee, blind to treatment allocation, reviewed all clinical end points and events resulting in switch to open label ZDV during the blinded phase, or initiation of ART during the open phase.

FOLLOW UP AND LABORATORY MEASUREMENTS

Children were assessed clinically at randomisation (week −2), at the start of trial drug (week 0), at 2, 4, 8, and 12 weeks, and then 12 weekly until the end of the blinded phase (October 1995). Monitoring for toxicity occurred throughout the blinded phase. Height, weight, full blood count, creatinine, AST or ALT, and CD4+ cell count were measured in the clinical centres at each visit. During the blinded phase, mean corpuscular volume (MCV) results were withheld from local investigators and transferred directly from the laboratory to the Trials Centres. Plasma was stored locally at −70°C. Adherence was assessed by questionnaire to caregivers and pill counts or returned bottles. After the blinded phase, clinical information and ART received were collected three monthly to December 1997 and then yearly.

END POINTS

The primary efficacy end point was the development of an AIDS defining event or death. Primary toxicity end points were serious clinical or laboratory events, categorised according to a paediatric modification of the National Cancer Institute Common Toxicity Criteria. Secondary end points were changes in CD4+ cell counts, height, and weight (adjusted for age); HIV-1 RNA viral load and ZDV resistance were evaluated in 70 children with available samples over a 96 week period during the blinded phase.

LABORATORY METHODS

T cell subsets were measured by flow cytometry in each clinical centre. HIV-1 RNA was measured using a quantitative reverse transcriptase polymerase chain reaction (RT PCR) assay (Amplicor Monitor, Roche Diagnostic Systems) from a single batch of kits in five laboratories, as described previously.[14] Zidovudine resistance associated point mutations at codons 41, 70, and 215 (M41L, K70R, T215Y/F) of the RT gene were assayed as described previously[15] in 49 children at baseline and 22 children on ZDV at 96 weeks. Resistance was defined as the presence of more than 5% mutant virus.

STATISTICAL ANALYSES

CD4 counts were expressed as absolute counts and percentages, and were adjusted for age by calculating CD4 z scores, based on data from uninfected children.[16] The two randomised groups were compared regardless of changes in treatment (intention to treat) in terms of time to AIDS or death using Kaplan–Meier plots, log rank test, and Cox proportional hazards models. The analyses were done separately for the blinded period and for the entire follow up to the end of December 1998. Adverse event analyses were restricted to time on, or within 30 days after stopping blinded therapy. The frequency of adverse events was compared between the randomised groups using the χ^2 test. Changes from baseline of CD4 counts, CD4 percent, CD4 z scores, HIV-1 RNA viral load, and height and weight adjusted for age[17] were compared between IMM and DEF using Wilcoxon rank sum tests for the average change as measured by the area under the curve minus baseline (AUCMB) to week 48. Two sided significance tests were used throughout.

The progression rates to AIDS or death for all children, regardless of treatment allocation during 1992–96 and 1997–98 (when combination therapies became more widely used) were estimated by fitting calendar time as a time dependent covariate and age at trial entry as a fixed covariate in a Cox proportional hazards model. These rates were used to compare the estimated cumulative AIDS free survival probabilities in the two calendar periods for a typical child, 4.1 years old (average age at trial entry), who survived and was AIDS free at one year after trial entry (follow up after one year in the trial occurred during both calendar periods, but no child was at risk of progression in the period 1997–98 during the first year of follow up in the trial).

Results

Between August 1992 and October 1995, 195 children were recruited. Three children were excluded from the analysis as they were not prescribed trial drug (in two, consent was

Table 1 Baseline characteristics

	IMM n = 102 (%)	*DEF n = 90 (%)*
Age (years)		
≤1	7 (6.9)	9 (10.0)
1–2	35 (34.3)	30 (33.3)
3–4	27 (26.5)	20 (22.2)
≥5	33 (32.4)	31 (34.4)
Sex: male	41 (40)	38 (42)
Ethnicity		
White	69 (67.7)	64 (71.1)
Black African	23 (22.5)	16 (17.8)
Other*	10 (10.0)	10 (11.1)
CDC clinical stage		
N	35 (34.3)	33 (36.7)
A	38 (37.3)	31 (34.4)
B	29 (28.5)	26 (28.9)
CD4 count/mm^3, median (IQR)	775 (463–1367)	935 (560–1340)
CD4%, median (IQR)	25 (17–33)	25 (19–31)
CD4 z score		
≤ −3	28 (27.5)	18 (20.0)
−3 to −2	17 (16.7)	14 (15.6)
−2 to −1	23 (22.6)	30 (33.3)
−1 to 0	21 (20.6)	17 (18.9)
≥ 0	13 (12.8)	11 (12.2)
HIV-1 RNA $\log_{10}$ copies/ml, median (IQR)	4.6 (3.6–5.1)**	4.6 (4.3–5.2)**

*Two Indian, 13 black/white Brazilian, two American Indian, one Indonesian, one white/black African, one unknown.
**69 children (34 IMM, 35 DEF).

withdrawn (1 IMM, 1 DEF) and one was found not to be HIV infected (IMM)). Only one child (IMM) was lost to follow up during the blinded phase. Twenty six children (18 IMM, eight DEF, of whom 18 were from the same country) were not seen after 30 June 1998; of these, nine (seven IMM, two DEF) had not been seen since 30 June 1997. Total follow up time during the blinded phase was 356 child years (187 IMM, 169 DEF), with a median of 1.9 (interquartile range (IQR) 1.4–2.7) years in IMM and 1.9 (IQR 1.3–2.9) years in DEF children. Total follow up (blinded and open phases) was 851 child years (442 IMM, 409 DEF), a median of 4.6 (IQR 3.6–5.5) years in IMM and 4.6 (IQR 3.6–5.8) years in DEF.

BASELINE CHARACTERISTICS

At randomisation, the mean age was 4.1 (SD 2.6) years; 42% were under 3 years, and 8.3% under 1 year (table 1). The median (IQR) CD4 count was 775 (463–1367) cells/mm^3 in IMM and 935 (560–1340) in DEF children; CD4 was 25% in both groups. There were 55 children in CDC category B,[10] of whom 32 (58%) had asymptomatic lymphocytic interstitial pneumonitits (LIP) and/or had experienced a single bacterial chest infection. Disease category distribution was similar in children followed throughout and those lost to follow up.

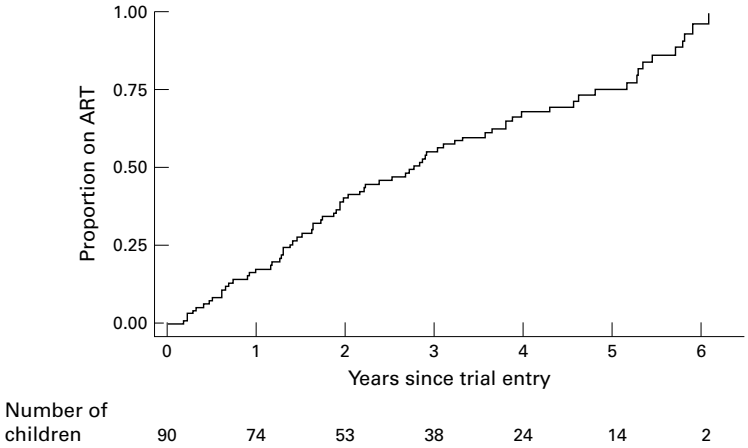

Figure 1 Time to starting any ART in the deferred group.

EXPOSURE TO ZDV AND OTHER ART

The median time to starting ART in the DEF group was 2.7 (IQR 1.3–4.1) years (fig 1). In the blinded phase, there was a substantial difference in the time spent on ZDV between the two groups (76% IMM; 13% DEF), and this was even greater if only the time before progression to AIDS was considered (77% IMM; 8% DEF). Median MCV was 77 (IQR 73–80) fl at baseline. By 24 weeks 78% of IMM and 10% of DEF children had an MCV more than three standard deviations above baseline.

During the blinded phase 21 (21%) IMM and 23 (26%) DEF children switched to open label ZDV (none were told of their original allocation at the time of switching). Reasons for switching were: development of AIDS (three IMM, seven DEF); other non-AIDS clinical progression (nine IMM, 11 DEF); falling CD4 counts (eight IMM, four DEF); at the request of parents (one IMM, one DEF).

After the blinded phase eight (8%) IMM switched immediately to didanosine (ddI) monotherapy and 26 (25%) added ddI, ddC, or 3TC; 48 (48%) subsequently switched to ddI or added a second or third NRTI (67% within 12 months); four (4%) who had stopped blinded therapy later started triple ART, and 15 never started open ART (14 had stopped ZDV and one had died during the blinded phase). Of the 90 DEF children, 29 (32%) started ZDV monotherapy (23 during and six after the blinded phase), of whom 27 subsequently added a second NRTI (n = 19), switched to ddI (n = 6), or switched to triple therapy (n = 2). Five (5%) children started monotherapy (four with ddI), and 39 (43%) started dual (n = 29) or triple (n = 10) ART as their initial regimen. Seventeen (19%) DEF children never received ART. Throughout follow up (average 4.6 years) the percentage time (including interruptions and stopping therapy) spent on no ART, monotherapy, two NRTI, or triple ART, with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI), was 21%, 44%, 29%, and 6% respectively in IMM and 62%, 12%, 18%, and 8% in DEF groups (fig 2).

CLINICAL, IMMUNOLOGICAL, AND VIROLOGICAL OUTCOMES

Four children (three IMM, one DEF) died during the blinded phase. In two (both IMM) children, death was HIV related (HIV encephalopathy; extrapulmonary tuberculosis) and in the third IMM child, the cause was unknown. The DEF child, who had HIV encephalopathy, died during an anaesthetic. During follow up, including the blind and open phases, 19 (12 IMM, seven DEF) children

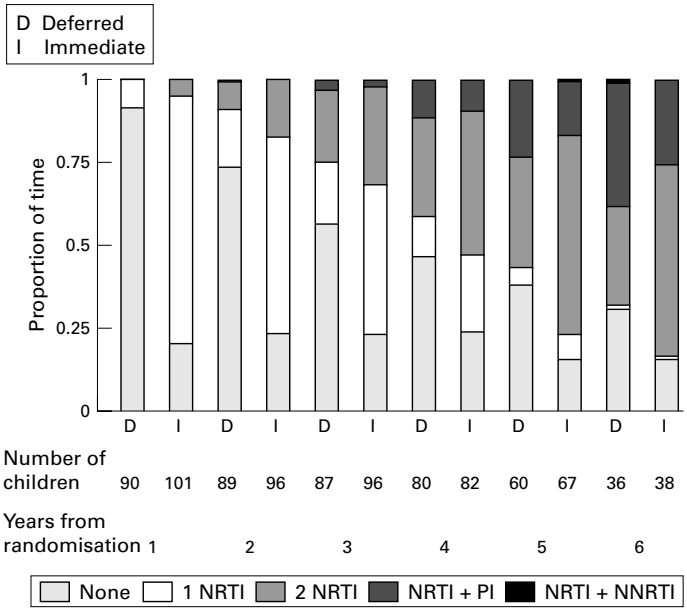

Figure 2 Proportion of time spent on different ART by time (in years) from randomisation.

died, 17 (11 IMM, six DEF) from HIV related causes.

During the blinded phase, eight IMM and 12 DEF children developed AIDS or died (hazard ratio of IMM to DEF 0.59 (95% confidence interval (CI) 0.24 to 1.43, p = 0.24). During overall follow up, 20 IMM and 21 DEF children progressed to AIDS or death (hazard ratio 0.92, 95% CI 0.50 to 1.70, p = 0.80).

Table 2 Hazard ratios IMM to DEF, for progression to AIDS and AIDS or death by year since randomisation

	AIDS		*AIDS or death*	
Year since randomisation	*Hazard ratio (95% CI) for IMM to DEF*	*p value*	*Hazard ratio (95% CI) for IMM to DEF*	*p value*
1	0.15 (0.02, 1.24)	0.08	0.29 (0.06, 1.45)	0.13
2	0.52 (0.12, 2.16)	0.36	0.50 (0.12, 2.11)	0.35
3	1.31 (0.37, 4.66)	0.67	1.73 (0.52, 5.76)	0.37
4	1.51 (0.36, 6.33)	0.57	1.49 (0.36, 6.24)	0.59
5	1.80 (0.16, 19.92)	0.63	1.76 (0.16, 19.45)	0.64

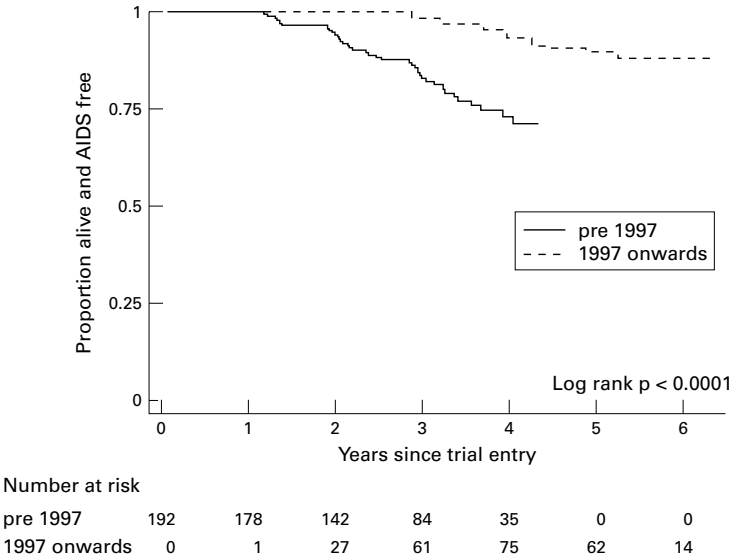

Figure 3 Time to AIDS or death for all children regardless of treatment allocation, by calendar time (pre/post December 1996).

Table 3 AIDS events (number of children) during overall follow up 1992–1998

	First event		*All events*	
Event	*IMM*	*DEF*	*IMM*	*DEF*
Opportunistic infections				
Pneumocystis carinii pneumonia	0	2	0 (0)	3 (3)
Cerebral toxoplasmosis	1	0	1 (1)	0 (0)
Mycobacteria avium intracellulare	1	0	1 (1)	1 (1)
Cytomegalovirus infection	0	0	2 (1)	0 (0)
Cryptococcal meningitis	0	1	0 (0)	1 (1)
Cryptosporidiosis	1	2	1 (1)	2 (2)
Oesophageal candidiasis	1	0	1 (1)	1 (1)
Extrapulmonary tuberculosis	1	0	1 (1)	0 (0)
Severe failure to thrive	7	11	8 (8)	12 (12)
Cardiomyopathy	0	0	1 (1)	0 (0)
Encephalopathy	1	2	1 (1)	2 (2)
Recurrent bacterial infections	1	2	1 (1)	2 (2)
B cell lymphoma	4	0	4 (4)	0 (0)
Kaposi's sarcoma	0	0	2 (1)	0 (0)
Total events (no. of children)	18 (18)	20 (20)	24 (18)	24 (20)

There was an early delay in progression to AIDS in favour of the IMM group during the first year of follow up, followed by a non-significant reversal of that trend in years 3 to 5 (table 2).

The commonest AIDS event was severe failure to thrive, accounting for 47% of first AIDS and 42% of all AIDS events (table 3). Opportunistic infections, encephalopathy, and recurrent bacterial infections occurred with similar frequency in IMM and DEF groups. All six children who developed malignancies were in the IMM group (p = 0.05).

There was no evidence that disease progression was significantly different in children under 3 years compared with those over 3 years of age at randomisation (26% versus 19%, p = 0.25). Progression to AIDS or death varied significantly with calendar period. In an analysis including all children alive and without AIDS one year after trial entry, regardless of treatment allocation, age adjusted progression was 6.6 per 100 child years during 1992–96 compared with 2.4 per 100 child years during 1997–98. The estimated AIDS free survival at three years from trial entry for a typical child age 4.1 years (the average age for children entering the trial) was 0.86 (95% CI 0.79 to 0.92) for follow up during 1992–96 compared with 1.00 during 1997 and 1998 (p < 0.0001, fig 3).

An initial increase in weight for age in the IMM compared with the DEF children during the blinded phase was not sustained (table 4, fig 4). Average change in CD4% as measured by AUCMB to week 48 was significantly greater in IMM but this was not significant to week 144. The average fall in $\log_{10}$ HIV RNA (measured by AUCMB) to week 24 was 0.28 in 35 IMM and 0.02 $\log_{10}$ copies/ml in 35 DEF children (p = 0.03). However, the difference to week 48 or to week 96 was not significant (table 4, fig 4).

ANTIRETROVIRAL RESISTANCE

One child (IMM) had a mutation (codon 41) at baseline. No children in the DEF group developed mutations while on placebo. Of 22 IMM children with samples available at

Table 4 Median (IQR) change from baseline to 48 weeks for immunological, virological, and clinical parameters

	Blinded phase, median (IQR) AUCMB, 0–48 weeks		
	IMM	DEF	p value
CD4 × 10^6/l	−64.1 (−42.2, 61.3)	−63.4 (−253.2, 44.1)	0.52
CD4%	0.5 (−2.9, 4.1)	−0.6 (−4.9, 2.1)	0.02
CD4 z score	−0.2 (−0.8, 0.3)	−0.3 (−0.9, 0.1)	0.21
Log_{10} HIV RNA*	−0.3 (−0.5, 0.05)	−0.04 (−0.3, 0.14)	0.06
Height (cm)	3.2 (2.1, 4.2)	3.0 (1.7, 4.6)	0.75
Height for age z score	0.01 (−0.17, 0.20)	0.05 (−0.2, 0.2)	0.81
Weight (kg)	1.0 (0.5, 1.5)	0.8 (0.3, 1.2)	0.05
Weight for age z score	0.06 (−0.12, 0.20)	−0.03 (−0.2, 0.2)	0.19

*On a subset of 69 (34 IMM, 35 DEF) children.

baseline and 96 weeks, PCR failed to amplify in six (all children of African origin). Of the other 16 children, two (13%) had no evidence of mutations; seven (44%) had single mutations at codon 215 (n = 2) or 70 (n = 5); seven (44%) had more than 5% mutant virus at 215, of whom two also had mutant virus at codon 70, and five at codon 41. High level (>50%) resistance at codons 215 and/or 41 was present in six (38%) children by 96 weeks.

ADVERSE EVENTS DURING THE BLINDED PHASE

Grade 3 or 4 neutropenia was the most frequent serious adverse event (seven events in four IMM; two events in two DEF). Two children in each group had grade 4 elevations of transaminases. Significantly more children in the IMM (n = 13) compared with the DEF (n = 3) group stopped therapy because of an adverse event (all grades, p = 0.02), most commonly because of neutropenia (three IMM, zero DEF), or nausea or vomiting (nine IMM, two DEF).

Discussion

PENTA 1 was set up to compare a policy of initiating ZDV monotherapy at the time of randomisation with that of waiting until the onset of symptoms in asymptomatic, vertically HIV infected children. Although nearly 8000 adults were randomised into nine trials addressing this question,[5] PENTA 1 provides the only data in children worldwide. At the time the trial commenced, disease progression in vertically infected children appeared to be considerably faster than in adults, particularly in the first year of life.[6–8] In children, CD4 count and CD4% decrease with age up to about 6 years,[16] and their predictive value for progression to AIDS and death in children is less clear.[18]

In this trial, despite a large difference in the amount of ZDV received between IMM and DEF groups, there was no evidence of benefit in favour of early ZDV monotherapy over an average of nearly two years, or over prolonged follow up to over 6.3 years (median 4.6 years). The latter is not surprising because of the increased use of ART in latter years. However, 19% of children had still not started ART by December 1998, and little time overall was spent on triple ART. With longer follow up, it may be possible to explore the benefits and disadvantages of receiving early sequential

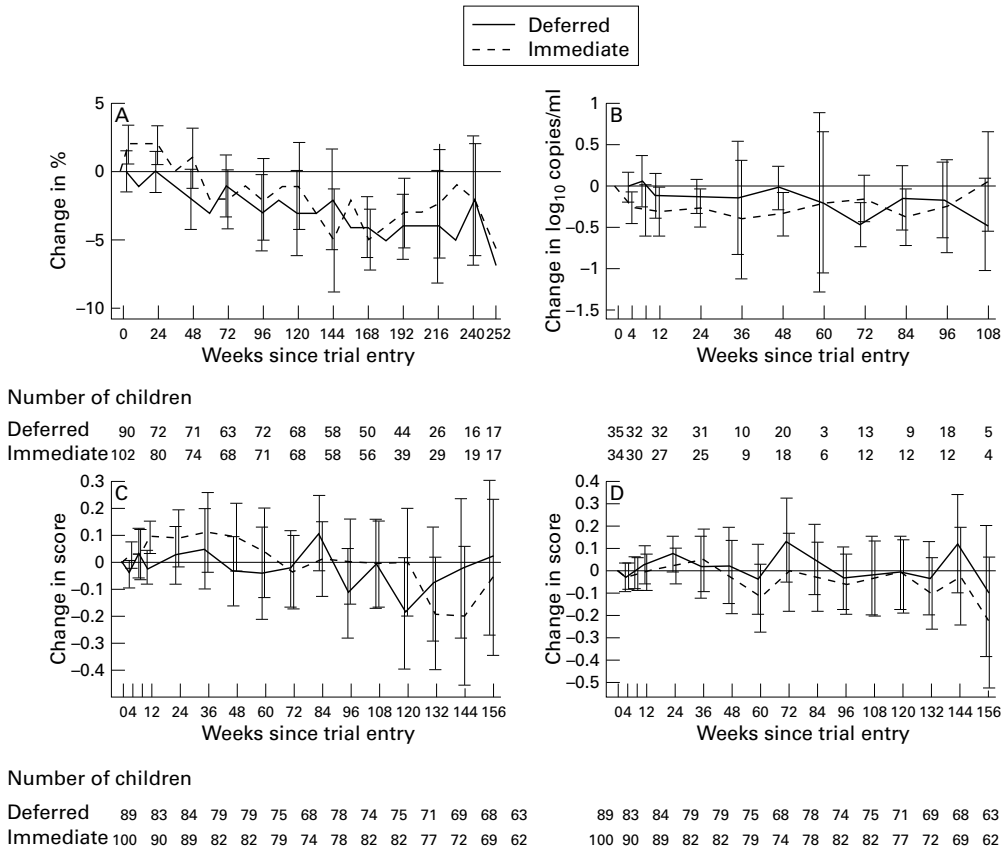

Figure 4 Median change (95% CI) from baseline in: (A) CD4%; (B) log_{10} HIV RNA; (C) weight for age; (D) height for age.

therapy versus initiating therapy later with triple ART.

As children developing AIDS in the first three months of life were not eligible, there was clearly a tendency to include those at lower risk of rapid disease progression in PENTA 1. This is likely to be the main reason for the lower overall progression rates observed, compared with cohort studies of vertically infected children followed from birth.[19 20] Disease progression rates after 12 months in the European Collaborative Study and French cohorts combined, and in children prospectively followed in the UK national surveillance scheme, are estimated to be about 5% per year.[21 22] This is similar to the estimated progression rate (to AIDS or death) of 14% at three years from trial entry observed in PENTA 1 during 1992–96. This is despite the fact that nearly one third of children had CDC stage B disease at trial entry. However, the majority had asymptomatic LIP, known to be associated with a relatively good prognosis.

The progression rate was significantly lower during 1997–98. This could not be explained by a "healthy survivor effect" as the comparison was made at the same time from trial entry and after adjusting for age at randomisation. The lower progression rate in later years is unlikely to be explained solely by the introduction of triple therapy, as the number of children on triple therapy during 1997 and 1998 in this trial was small. Benefit may have been largely a result of increased dual ART received during later years.

The most common AIDS event, accounting for over 47% of first AIDS diagnoses, was severe failure to thrive. Similar findings were reported from the PACTG 152[23] and PACTG 300 trials.[24] In PENTA 1, opportunistic infections accounted for 26% of first AIDS diagnoses, whereas recurrent bacterial infections were relatively uncommon, possibly because nearly half the children in PENTA 1 continued to receive trimethoprim–sulphamethoxazole prophylaxis after 12 months of age.[25] Although small numbers, all six malignancies occurred in the IMM group. This is likely to be a chance finding, as data from adult trials do not suggest any association between ART exposure and malignancy rates. In contrast to the PACTG 152 trial where neurological deterioration was the second most frequently reported endpoint,[23] only three children in this trial developed HIV encephalopathy. A strict definition was adopted which did not include minor neurodevelopmental abnormalities in this culturally diverse population speaking many different languages.

The difference in HIV RNA between children on ZDV and placebo was relatively small. After two years of ZDV, the proportion of IMM children with high level (>50%) resistance to ZDV was quite low (38%), and 13% had no ZDV associated mutations. Over 60% of adults on ZDV monotherapy were reported to develop high level resistance at these codons after 2.5 years on therapy in the Concorde trial, although numbers were also small.[26] Adherence could account for these findings, but MCV changes among children in the IMM group were similar to those reported in the adult Concorde trial.[4]

The question of when to start ART in children has not been resolved by this trial. It provides no information about the optimal timing of commencement of combination therapies, which are now standard of care. US paediatric guidelines recommend starting ART in all infants diagnosed in the first year of life.[27] However, there are potential disadvantages to this approach as, especially in infancy, treatment options are limited and problems of adherence are considerable. In adults it has been argued that potent ART given too early may decrease the natural immune response to HIV.[28]

Our data show that after 3 months of age, many vertically infected children have slow progression of disease, in the absence of therapy. With uncertainties about long term efficacy and toxicity, a case can be made for delaying ART in the well asymptomatic child. Furthermore, preliminary data suggest that even children with advanced disease and very high viral loads have dramatic increases in CD4 counts following potent ART, and the majority of CD4+ cells are naïve (CD45+RA+ cells).[29] The theoretical benefits of early therapy in preventing immune suppression in adults could be less important in children as they have a functioning thymus. As more trials investigate ways of using currently available drugs and evaluate new drugs, more potent and acceptable regimens may well become available for children in the future, and this may be to the advantage of children who have not yet started ART. It is important that information on ART history is collected along with clinical, immunological, and virological data, in order to interpret changes in disease progression over time. Long term follow up of all children enrolled in this and other PENTA trials is planned.

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Appendix

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