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Three year follow-up of the PENTA 5 Trial

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Abstract (updated)

Background: PENTA 5 was a 48 week prospective randomised controlled trial comparing 3 dual NRTI combinations with or without NFV as first ART therapy. We describe long term response to 160 weeks.

Methods: 128 children were randomised to ZDV+3TC (n=36), ZDV+ABC (45) or 3TC+ABC (47). Asymptomatic children (n=55) were also factorially randomised to NFV or placebo; all other children received open-label NFV. 1 child was lost to follow-up and 1 died before 2 weeks: data on the remaining 126 children are presented. Analyses are intent-to-treat.

Results: Median follow-up was 176 weeks (IQR 161-203). Two children had new AIDS events after 48 weeks (encephalopathy week 92, extrapulmonary TB week 123) and 1 child died without AIDS (week 164); although 2/3 had completely switched ART, none ever achieved RNA <400 c/ml and all had CD4%<15% at the time of the event. At 3 years, 2/116 (2%) children were reported as having clinical signs of lipodystrophy: both had been taking 3 drug regimens with NFV for >140 weeks. At 160 weeks 56%, 55% and 59% were still on randomised therapy in the ZDV+3TC, ZDV+ABC and 3TC+ABC groups (including NFV/no NFV as randomised: dual NRTI alone for 13 children). 67%, 64% and 72% were on randomised NRTI combinations in the 3 NRTI groups respectively. Excluding single drug switches for toxicity in the first 8 weeks, 36% ZDV+3TC, 25% ZDV+ABC and 17% 3TC+ABC had changed 1 or more drugs when HIV-1 RNA was >400 c/ml (logrank p=0.15). Of 120 (95%) children with HIV RNA measured at week 160, 54% ZDV+3TC, 48% ZDV+ABC and 70% 3TC+ABC had RNA<400 c/ml (p=0.07 adjusted for minor baseline imbalances and receipt of NFV/placebo), with 37%, 31% and 40% <50 c/ml respectively (adjusted p=0.8). Corresponding decreases in log_{10} RNA were 2.4, 2.4 and 3.1 respectively (p=0.08). Among children randomised to and still taking dual NRTI alone, 0/2 ZDV+3TC, 4/6 ZDV+ABC and 4/5 3TC+ABC had RNA<400 c/ml. Median increase in height for age Z-score was 0.20, 0.21 and 0.51 (p=0.03), reflecting RNA response at week 160; and increase in CD4% was 11%, 11% and 10% respectively (p=0.3).

Conclusions: By 160 weeks, 44% children had made at least 1 change to randomised regimen for toxicity, lack of response, compliance or other reasons. However, improved efficacy (in terms of HIV-1 RNA suppression and growth changes) and lower rates of switching with detectable HIV-1 RNA in the 3TC+ABC group were sustained from 48 to 160 weeks. Clinical evidence of lipodystrophy was reported in only 2 (2%) children.

Background & Objectives

PENTA 5 was a 48 week randomised controlled trial comparing 3 dual nucleoside analogue reverse transcriptase inhibitor (NRTI) combinations, with or without nelfinavir (NFV), as first line antiretroviral therapy[1].

To investigate longer term response with these NRTI combinations, we analysed changes in CD4 and plasma HIV-1 RNA to 160 weeks together with changes in antiretroviral therapy (ART).

PENTA 5 trial design

- 128 ART-naive children were randomised to ZDV+3TC (n=36) or ZDV+ABC (n=45) or 3TC+ABC (n=47).
- Asymptomatic children (n=55) were also randomised to receive nelfinavir (NFV) or NFV placebo (Part A): and all other children (n=73) received open label NFV (Part B).
  - children in Part A were unblinded to NFV/placebo allocation when the last child enrolled reached 24 weeks of follow-up (25 October 1999), and continued or changed their current regimen depending on the decision of their paediatrician
- At baseline, median age was 5.3 years (range 0.3-16.7 years), median CD4% was 22% (IQR 15-29%), mean HIV-1 RNA was 5.0 log_{10} copies/ml (SD 0.8); 12 children (9%) had had an AIDS defining event

Results to week 48[1]

One child was lost to follow-up after 3 days, and one died from sepsis in the first month after starting 3TC+ABC+NFV in Part B. All other children were followed beyond week 48 for the primary analysis. 4 children developed a new AIDS defining event before 48 weeks (1 ZDV+3TC, 2 ZDV+ABC, 1 3TC+ABC).

At both 24 and 48 weeks after initiation of ART, ABC containing regimens were more effective than ZDV+3TC in terms of absolute reduction in log_{10} HIV-1 RNA and proportions with HIV-1 RNA below 400 copies/ml[1]. Improved virological control in the NFV group at week 24 had attenuated at week 48, possibly as a result of sub-optimal dosing.

All regimens were generally well tolerated and the incidence of hypersensitivity to ABC (3%) was similar to that observed in adults.

Statistical methods

All analyses are intention to treat. Baseline values were those before and nearest to randomisation (within 4 weeks). Changes from baseline were based on the closest value to nominal assessment weeks (within equally spaced windows). For HIV-1 RNA below the lower limit of quantification (<50 copies/ml), normal interval regression was used, replacing values with the interval in which the true value could lie (the interval [0,50] copies/ml). Proportions were compared using exact tests.

Because of minor imbalances in baseline characteristics and receipt of NFV in the NRTI groups, analyses were also adjusted for age, HIV-1 RNA and CD4% at baseline; plus allocation to NFV in Part A or Part B or placebo in Part A for NRTI comparisons[1]. 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 uninfected children.

Follow-up & clinical events

- All 126 children with follow-up at 48 weeks were followed beyond 48 weeks (36 ZDV+3TC, 44 ZDV+ABC, 46 3TC+ABC). Median follow-up to 31 December 2002 was 180 weeks (IQR 162-204, range 97-245 weeks).
  - only 2 children were last seen alive before 144 weeks (at 97 and 104 weeks respectively)

After week 48

- 2 children had new AIDS events (encephalopathy week 92, extrapulmonary TB week 123)
- 1 child died without AIDS at week 164 (following Hodgkin's lymphoma)
  - although 2/3 had completely switched ART, none ever achieved RNA <400 copies/ml and all had CD4%<15% at AIDS/death
- ★ from 0-160 weeks, total new AIDS events or death: 2 ZDV+3TC, 3 ZDV+ABC, 3 3TC+ABC
- at the 3-year follow-up, clinical signs of lipodystrophy reported in 2/116 (2%)
  - both white, on 3 drug regimens with NFV for >140 weeks
  - aged 8.6 and 3.6 years at ART initiation with ZDV+3TC+NFV and ZDV+ABC respectively

ART to 160 weeks

- At 160 weeks, 56% children were still taking their randomised NRTI including NFV/no NFV as randomised (Table 1).
  - a further 11% children had not changed their NRTI combination (eg added NFV or switched NFV to NNRTI or other PI)

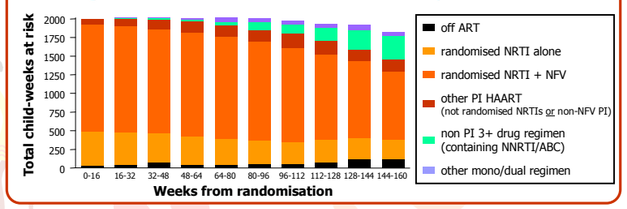
Therefore overall to week 160 the majority of child-time on trial was spent taking NRTI combination as randomised (Figure 1).

- Excluding early single drug switches for toxicity, marginally more children in the ZDV+3TC group had changed 1 or more drugs when HIV-1 RNA was >400 copies/ml (logrank p=0.14) (Table 1)
  - a number of ART changes after week 48 occurred when children had suppressed HIV-1 RNA (because of concerns about toxicity, pill burden or the desire to construct easier regimens) and resistance is not likely to have developed
- ddI+d4T+EFZ was the most popular regimen not based on the trial NRTI combinations (n=10)`

Table 1: ART at 160 weeks

	ZDV+3TC n=36	*(100%)*	ZDV+ABC n=44	*(100%)*	3TC+ABC n=46	*(100%)*
on randomised NRTI AND NFV/no NFV as allocated	**20**	***(56%)***	**24**	***(55%)***	**27**	***(59%)***
on randomised NRTI	**24**	***(67%)***	**28**	***(64%)***	**33**	***(72%)***
changed ≥1 drugs when RNA was >400 copies/ml	**13**	***(36%)***	**11**	***(25%)***	**8**	***(17%)***
off ART	**0**		**5**	***(11%)***	**3**	***(7%)***

Figure 2: Child-time to 160 weeks by ART taken



Children randomised to dual NRTI

7 ZDV+3TC, 11 ZDV+ABC and 6 3TC+ABC were randomised to placebo in Part A

- at week 160
  - 2/7 (29%) were still taking ZDV+3TC only
    - *0/2 had HIV-1 RNA <400 copies/ml*
  - 6/11 (55%) were still taking ZDV+ABC only
    - *4/6 had HIV-1 RNA <400 copies/ml (all <4000 c/ml)*
  - 5/6 (83%) were still taking 3TC+ABC only
    - *4/5 had HIV-1 RNA <400 copies/ml (all <4000 c/ml)*
  - remaining children had added NFV or switched ART completely

HIV-1 RNA at and to 160 weeks

The decline in HIV-1 RNA at 48 weeks was sustained to week 160 (Figure 2(a)), but the difference between the NRTI groups was smaller (Figure 2(b))

- more children in the ZDV+3TC group had switched to second-line therapies for lack of virological response or virological failure.

Overall results at 160 weeks continued to suggest superiority of 3TC+ABC.

Although similar proportions had HIV-1 RNA <400 copies/ml at weeks 48 (60%) and 160 (58%), at week 160 fewer children had <50 copies/ml (36%) than week 48 (44%).

However, some tests at 160 weeks were <400 copies/ml on standard assays and are conservatively considered NOT <50 copies/ml (1 ZDV+3TC, 4 ZDV+ABC, 4 3TC+ABC).

Figure 2(a): Changes in log_{10} HIV-1 RNA (unadjusted)

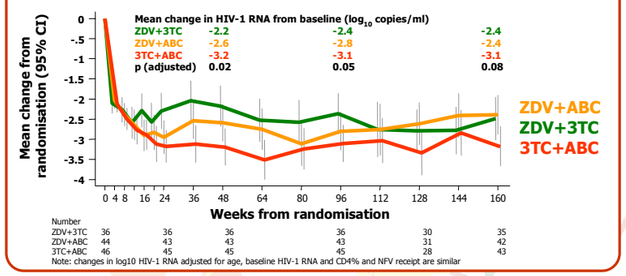
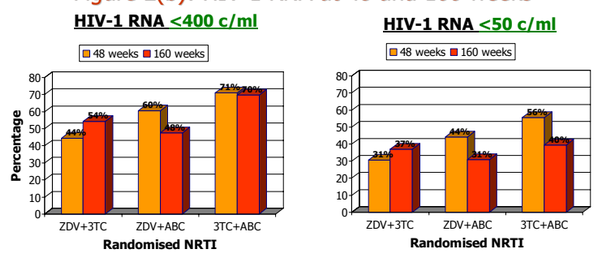


Figure 2(b): HIV-1 RNA at 48 and 160 weeks



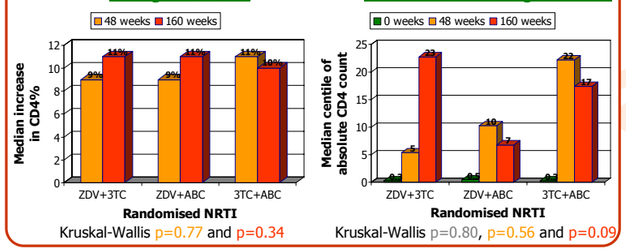
Adjusted global p=0.05 and p=0.07 | Adjusted global p=0.10 and p=0.8

CD4, height and weight at 160 weeks

Changes in CD4%, absolute CD4, age-adjusted CD4 Z score, height-for-age and weight-for-age at 160 weeks broadly mirrored the changes observed at 48 weeks (Figures 3 and 4).

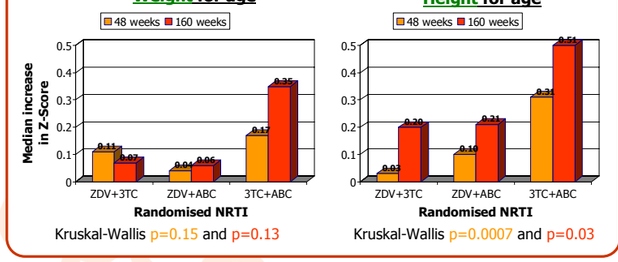
- in spite of differences in HIV-1 RNA response, increases in CD4% were similar in all 3 groups and had plateaued between 48 and 96 weeks
  - at 160 weeks increases in CD4% were 11% on average
- Height-for-age continued to increase significantly between 48 and 160 weeks.
- Significant differences in height-for-age at both 48 weeks and 160 weeks reflected reductions in HIV-1 RNA across the NRTI groups at these timepoints.

Figure 3: CD4% and Z-score at 48 and 160 weeks



Kruskal-Wallis p=0.77 and p=0.34 | Kruskal-Wallis p=0.80, p=0.56 and p=0.09

Figure 4: Growth and weight at 48 and 160 weeks



Kruskal-Wallis p=0.15 and p=0.13 | Kruskal-Wallis p=0.0007 and p=0.03

Summary

- ★ 56% children had not changed from allocated therapy at 160 weeks
  - many children stayed on their allocated regimens in spite of detectable viral load
  - this is likely to be due to difficulties in achieving and sustaining virological suppression <400 copies/ml, problems with PK and sub-optimal dosing, and uncertainty at what levels of HIV-1 RNA at which to switch as well as sustained clinical and immunological well-being
- ★ Fewer children switched from ABC containing regimens when HIV-1 RNA was above 400 copies/ml
- ★ Improved efficacy of 3TC+ABC in terms of HIV-1 RNA suppression and growth changes was maintained from 48 to 160 weeks
- ★ CD4% increased slightly between 48 and 160 weeks; but there were no differences in the CD4% increase between the NRTI combinations
- ★ clinical evidence of lipodystrophy was reported in only 2% children

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(1) Paediatric European Network for Treatment of AIDS (PENTA). *Lancet* 2002; **359**:733-40.