96 week follow-up of the PENTA 5 trial; comparing ZDV+3TC, ZDV+ABC and 3TC+ABC, with or without NFV in ART naive children

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Background & Objectives

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

To investigate longer term response with these NRTI backbones, we analysed changes in CD4 and plasma HIV-1 RNA to 96 weeks together with switches 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)
- Children with early disease (n=55) were also randomised to receive nelfinavir (NFV) or NFV placebo (Part A): and all children with more advanced disease (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)

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 AIDS

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 treatment (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 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 or placebo in Part A or Part B 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

Follow-up to week 96

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 2001 was 148 weeks (IQR 128-163, range 90-199 weeks).

- 123/126 (98%) contributed an HIV-1 RNA measurement to week 96 (92% within ±12 weeks)
- 119/126 (94%) contributed a CD4 measurement to week 96 (87% within ±12 weeks)

No new AIDS defining events or deaths occurred between 48 and 96 weeks.

ART at and to 96 weeks

At 96 weeks, 72% 84% and 83% children in the ZDV+3TC, ZDV+ABC and 3TC+ABC groups were still taking their randomised NRTI (Table 1).

- More children in the ZDV+3TC group had switched NRTI backbone completely or added new NRTIs to their backbone, mostly because of lack of virological response or virological failure (none of the ZDV+3TC group had switched to 3TC+ABC)
- In contrast, most switches from ABC were for definitive (n=2) or possible (n=3; subsequently not confirmed) hypersensitivity reactions within the first 4 weeks

Overall, at 96 weeks in the ZDV+3TC, ZDV+ABC and 3TC+ABC groups

- 11%, 18% and 17% were taking their randomised dual NRTI only
- 61%, 64% and 65% were taking their randomised dual NRTI plus NFV
- 19%, 16% and 11% were taking another 3 drug (HAART) regimen
- 6%, 0% and 2% were taking another mono or dual regimen

Therefore overall to week 96 the majority of child-time on trial was spent taking NRTI backbone as randomised (Figure 1)

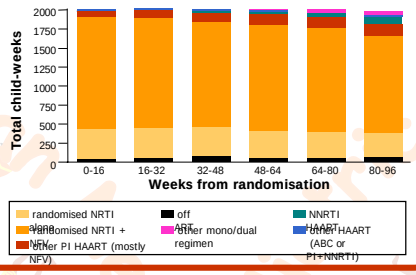
Table 1: NRTI backbone at 96 weeks

	ZDV+3TC	ZDV+ABC	3TC+ABC
no NRTI	2 (6%)	1 (2%)	2 (4%)
randomised NRTI	26 (72%)	37 (84%)	38 (83%)
switch 1 NRTI to other trial NRTI		5*(11%)	3* (7%)
switch ZDV→d4T	1 (3%)	1 (2%)	
add 3rd NRTI	1 (3%) (add ddI)		1 (2%) (add ZDV)
new NRTI regimen			
ddI+d4T	5 (14%)		2 (4%)
d4T	1† (3%)		
Total	36 (100%)	44 (100%)	46 (100%)

* 5 children (3 ZDV+ABC, 2 3TC+ABC) switched ABC , changing their NRTI backbone to ZDV+3TC, 2 ZDV+ABC switched to 3TC+ABC, and 1 3TC+ABC switched to ZDV+ABC.
† in combination with 1 NNRTI plus 1 PI

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

Figure 1: Child-time to 96 weeks by current therapy



Children randomised to dual NRTI

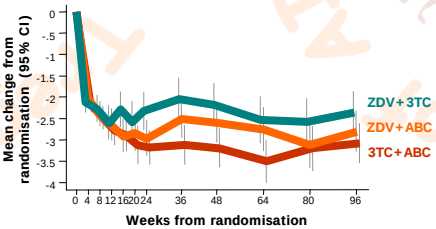
In Part A, 82% and 75% child-time in NFV and NFV placebo groups to 96 weeks was spent on or off NFV respectively.

Of 7/11/6 children randomised to placebo in Part A in the ZDV+3TC, ZDV+ABC and 3TC+ABC groups; at week 96

- 2/8/5 were taking their randomised dual NRTI only
  - *of whom 1/6/3 had HIV-1 RNA <400 copies/ml (all <6000 copies/ml)*
- 1/2/1 were taking their randomised dual NRTI only plus NFV
  - *of whom 0/1/1 had HIV-1 RNA <400 copies/ml (all <5000 copies/ml)*
- 4/1/0 were taking other therapy
  - *of whom 2/0/0 had HIV-1 RNA <400 copies/ml*

HIV-1 RNA at and to 96 weeks

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



Number								
ZDV+3TC	36	33	36	30	36	26	26	36
ZDV+ABC	44	37	43	36	43	30	38	42
3TC+ABC	46	41	45	36	45	33	31	45

Note: changes in log10 HIV-1 RNA adjusted for age, baseline HIV-1 RNA and CD4% and NFV receipt are similar

- The decline in HIV-1 RNA at 48 weeks was sustained to week 96 (Figure 2), but the difference between the NRTI groups was smaller compared to week 48 (Table 2)
  - more children in the ZDV+3TC group in particular had switched to second-line therapies for lack of virological response or virological failure (Table 1).
- Overall results at 96 weeks continued to suggest superiority of ABC containing regimens (Table 2).
- Although similar proportions had HIV-1 RNA <400 copies/ml at weeks 48 (60%) and 96 (61%), fewer children had <50 copies/ml at week 96 (37%) than week 48 (44%), illustrating the difficulties in sustaining complete virological control in children.
- In Part A, 57% and 55% children in the NFV and NFV placebo groups respectively had HIV-1 RNA<400 copies/ml at 96 weeks (adjusted p=0.7), with 25% and 32% respectively <50 copies/ml (adjusted p=0.7), corresponding to a decrease of 2.4 and 2.3 in log $_{10}$ HIV-1 RNA respectively (p=0.7).

Table 2: HIV-1 RNA at 96 weeks

	ZDV+3TC (n=36)	ZDV+ABC (n=43/42)	3TC+ABC (n=45)	Adjusted global p
N (%) ≤400 c/ml				
- 48 weeks	16 (44%)	26 (60%)	32 (71%)	0.05
- 96 weeks	18 (50%)	25 (60%)	32 (71%)	0.09
N (%) ≤50 c/ml				
- 48 weeks	11 (31%)	19 (44%)	25 (56%)	0.10
- 96 weeks	12 (33%)	14 (33%)	19 (42%)	0.38
Mean* drop in $\log_{10}$ HIV-1 RNA				
- 48 weeks	1.7	2.2	2.6	0.02
- 96 weeks	2.2	2.8	3.0	0.05

* estimated for a child with median age (5 years), CD4% (22%) and HIV-1 RNA (5.1 $\log_{10}$ copies/ml) at baseline, receiving placebo in Part A

CD4, height and weight at 96 weeks

Changes in CD4%, age-adjusted CD4 Z score, height-for-age and weight-for-age at 96 weeks also broadly mirrored the changes observed at 48 weeks (Table 3).

Interestingly, significant differences in height-for-age at both 48 weeks and 96 weeks reflected reductions in HIV-1 RNA across the NRTI groups at these timepoints.

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Table 3: CD4, height and weight at 96 weeks

Median unadjusted change in	ZDV+3TC	ZDV+ABC	3TC+ABC	K-Wallis global p
CD4 %				
- 48 weeks	+9	+9	+9	0.80
- 96 weeks	+11	+8	+12	0.27
Height for age				
- 48 weeks	+0.03	+0.10	+0.29	*0.0007*
- 96 weeks	+0.22	+0.42	+0.53	*0.03*
Weight for age				
- 48 weeks	+0.15	-0.03	+0.17	0.09
- 96 weeks	+0.10	+0.17	+0.37	0.24

Regimen failure by 96 weeks

★ In children who suppressed HIV-1 RNA <400 copies/ml, time to subsequent virological failure (>2000 copies/ml) was longest in the 3TC+ABC group (logrank p=0.03)

41%, 52% and 22% of children suppressing HIV-1 RNA <400 copies/ml in the ZDV+3TC, ZDV+ABC and 3TC+ABC groups respectively had rebounded

★ Time to the first new second line regimen (containing none of the drugs in the original treatment allocation) **OR** stopping all ART for at least 8 weeks was shorter in the ZDV+3TC group (logrank p=0.01)

22%, 2% and 9% children in the ZDV+3TC, ZDV+ABC and 3TC+ABC groups respectively had started a completely new regimen or stopped all therapy

★ Considering switch to new regimens, stopping all ART and virological failure together, the 3TC+ABC group tended to have the most durable suppression (exact p=0.11, Table 4).

★ Whilst by 96 weeks, children in all groups had been exposed to a median of 3 antiretroviral drugs, the maximum was 9, 4 and 6 in the ZDV+3TC, ZDV+ABC, 3TC+ABC groups respectively (Kruskal-Wallis p=0.30).

Table 4: Virological failure and regimen change by 96 weeks

	ZDV+3TC	ZDV+ABC	3TC+ABC
new second line regimen OR stopped all ART for ≥8 weeks OR HIV-1 RNA >2000 c/ml after suppression <400 c/ml	17 (47%)	22 (50%)	12 (26%)
HIV-1 RNA ≤2000 c/ml after suppression <400 c/ml whilst staying on at least 1 drug from the original regimen	15 (42%)	19 (43%)	30 (65%)
HIV-1 RNA never <400 c/ml whilst staying on at least 1 drug from the original regimen	4 (11%)	3 (7%)	4 (9%)
Total	36 (100%)	44 (100%)	46 (100%)

Summary

- A large proportion of children were still taking their randomised NRTI backbone at 96 weeks
  - 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 meant that many children stayed on their allocated regimens in spite of detectable viral load
- Fewer children switched from ABC containing regimens for virological failure or lack of virological response
- Improved efficacy of ABC containing regimens in terms of HIV-1 RNA suppression and growth changes was maintained from 48 to 96 weeks
- CD4% continued to increase slightly between 48 and 96 weeks; but there were no differences in the CD4% increase across the NRTI backbones

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