Does Early Treatment Provide Long Term Benefit in HIV-1 Infected Infants ? Five Year Outcomes in Children Treated Before 3 Months of Age in the PENTA 7 Trial.

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Abstract R-151

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Abstract

Background: Treating HIV-1 infected infants early after birth remains a crucial issue. Guidelines from different countries differ in whether to start immediate or differed therapy in asymptomatic children <12 months of age. In PENTA 7, 20 infants received ddI+d4T+Nelfinavir before 3 months of age. Clinical and immunological benefit was seen at 18 months. However virologic failure and emergence of resistance was a major concern. We describe long-term response to 5 years. **Methods:** Nineteen children (1 died at week 60 of non-HIV causes) were followed beyond 18 months. HIV events, CD4 cell counts and percentages, HIV-1 RNA, ART received, weight and height measurements were collected every 3 months between 18 months and 3 years and annually beyond 3 years. Changes in CD4, height and weight z-scores from baseline were assessed using the paired Wilcoxon signed rank test. **Results**: Median follow-up was 5.2 years (IQR 5.0–5.9). All children were seen at least at 5 years except one (consent withdrawn after 3.8 years of follow-up). No AIDS events were reported. Two children were still on initial therapy and four had stopped antiretroviral therapy permanently. Thirteen children switched to second (11) or third (2) line regimen using 2 new drugs (6 children), 3 (5) or 4 (2) including ZDV (2), 3TC (10), ABC (5), FTC (1), LPV/r (9), EFV (4) or NVP (4). Changes were due to lack of viral load response (6), resistance mutations (3) or other (4). Among the 18 children analysed, 10 had a viral load < 400 cp/mL (7 < 50 cp/mL). Median viral load of the eight remaining children was relatively low at 2570 cp/mL (range 479 to 44300 cp/mL). The proportion of children <400 cp/mL (56%) was similar to that observed at 18 months (47%). Median CD4% was 31% (range 22–44), with median increase from baseline in CD4 z-score +0.66 (IQR –0.9 to 1.5, p=0.19). Weight and height adjusted for sex and age had increased significantly by 5 years (median increase z-score from baseline +0.90 and +0.98, respectively, both p=0.002). **Conclusions:** By 5 years, children did not show any major clinical progression, maintained good level of CD4% and stable viral load. Growth improvement found at 18 months was sustained through long term follow-up. While most of the children switched to 2nd or 3rd line regimen, new resistance mutations were reported in few children. Starting HAART early in life with more potent, suitable and palatable drugs may prevent early switches and thus preserve future drug options.

Background

Treating HIV-1 infected infants early after birth remains a crucial issue. Guidelines from different countries differ in whether to start immediate or differed therapy in asymptomatic children <12 months of age. In PENTA 7, 20 infants received ddI+d4T+Nelfinavir before 3 months of age. Clinical and immunological benefit was seen at 18 months. However virologic failure and emergence of resistance was a major concern. We describe long-term response to 5 years.

Trial Design and Methods

Phase I/II, non randomised study to assess the toxicity, tolerability and activity of triple therapy ddI+d4T+Nelfinavir in vertically HIV-1 infected children aged less than 3 months.

• Clinical events, CD4 cell counts and percentages, HIV-1 RNA, antiretroviral therapy, weight and height measurements were collected every 3 months between 18 months and 3 years and annually beyond 3 years.

Results (Follow up, Events, ART, HIV-1 RNA, CD4, growth)

BASELINE CHARACTERISTICS

Sex	Female ; Male	9 ; 11
Ethnic origin	White	9
	Black African	9
	Black carribean	1
	Other	1
Median (range) age in months		2.6 (0.9 - 4.7)
Median (range) weight (kg) at birth		3.0 (0.7 - 3.6)
Median (range) weight (kg) at trial entry		4.8 (1.7 - 6.2)
CDC stage at entry	N ; A ; B	12 ; 5 ; 3
Median (IQR) log 10 HIV-1 RNA		5.5 (5.4 - 6.2)
Median (IQR) CD4 %		33 (24 - 46)

FOLLOW UP, EVENTS

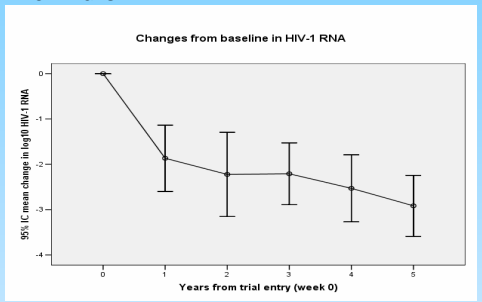
- Median follow up : 5.2 years (IQR 5.0–5.9)
- 1 death (Not HIV related)
- 1 withdrawn consent at 3.8 years
- 18 children evaluable at 5 years
- No AIDS events
- No major toxicity
- No clinical lipodystrophy reported

ART RECEIVED

	Total
Children enrolled in the study	20
Number of different drugs ever received median [range]	
All classes	5 [3, 8]
NRTI	3 [2, 5]
PI	2 [1, 3]
NNRTI	1 [0,1]
Number of children exposed to:	
All 3 classes	4 (20 %)
NRTIs + PIs only	12 (60 %)
NRTIs + NNRTIs (excl NFV)	4 (20 %)
Number of changes in ART triple therapy prescribed at week 0	
0	7 (35 %)
1	0 (0 %)
2	4 (20 %)
3	7 (35 %)
4	1 (5 %)
5	1 (5 %)

On the 18 children with ART assessment at 5 years or more, 4 were off therapy, 2 on first regimen, 12 had switched to second line (10) or third line therapy (2).

CHANGES IN HIV-1 RNA

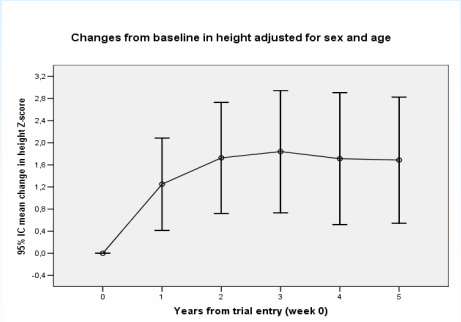


HIV-1 RNA still continued to decrease by 5 years of follow-up. The mean (range) change in $\log_{10}$ HIV-1 RNA from baseline was 2.9 (0.9 – 5.1) and half of the children were under 400 copies/ml.

CHANGES IN CD4 %, CD4 ADJUSTED BY AGE

By year 5, CD4% values ranged from 22% to 44%. The median increase in CD4 z-score change from baseline was +0.66 (range -5.29 to 3.76, p=0.19).

CHANGES IN HEIGHT AND WEIGHT Z-SCORES



Height and weight changes from baseline adjusted for sex and age increased significantly over time. Growth improvement found at 18 months was still sustained at year 5 (median increase z-score from baseline +0.90 and +0.98, respectively, both p=0.002).

Discussion

Early treament in HIV-1 infected children is recommended in several guidelines as it can prevent immune deterioration and severe clinical progression. In the PENTA 7 study, infants treated with d4T+ddI+NFV before 3 months of age showed a good clinical and immunological improvement and no major toxicity. Despite a rapid decrease in HIV-1 RNA, viral load was not completely suppressed with the subsequent emergence of resistance mutations. Difficulties in administration of this initial regimen and pharmacokinetic issues of NFV were probably the main reasons for a poor virological response.

At 5 years, no AIDS progression or severe stage B were reported and no clinical lipodystrophy was detected by clinicians. From 19 children alive, 1 withdrew consent at 3.8 years. Out of the remaining 18, 2 were still on their initial regimen and 4 discontinued drugs permanently (3 for poor compliance and 1 who was completely suppressed due to parent's request). The majority of children who had switched from the trial therapy are on second line therapy either on PI based regimen (6) or NNRTI (4). Only 2 children are on third line therapy and receive both PI and NNRTI.

No additional resistance mutations were reported after initial switches. Futhermore, all evaluable children have relative stable HIV-1 RNA. The proportion of children with VL< 400 copies/ml (56%) is slightly better than that observed at 18 months (47%). Immunological improvement observed at 3 years was maintained at 5 years with a median CD4% of 31%. Children are growing well and changes in height and weight z-scores are still statistically significant at 5 years.

Conclusion : Children treated very early in life in this non comparative study are still experiencing clinical and immunological benefit of HAART at 5 years but the majority of them are not taking the initial regimen. Initial regimen with potent, palatable and more suitable formulations may prevent early switches and preserve future options. Cardiovascular and metabolic studies in children exposed very early in life are necessary to establish long term toxicity.

Participants

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