Three year outcomes in children treated with HAART before 3 months of age in the PENTA 7 trial

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Background:

The use of highly active antiretroviral therapy (HAART) has dramatically reduced mortality and morbidity in HIV-infected adults and children. Data from US and European cohorts showed that progression to AIDS or death during the first year of life was present in 20-25% of untreated babies [1]; very high HIV-1 viral load (VL) during primary infection and immaturity of the immune system for bringing viral replication under control provided the rationale for immediate initiation of HAART in primary HIV-1 vertically infected infants [2]. PENTA 7 was a 72 week phase I/II, non randomised study to assess the toxicity, tolerability and activity of stavudine, didanosine and nelfinavir in vertically HIV-1 infected infants. Virological failure was defined as HIV-1 RNA levels > 400 copies/ml on two successive occasions after 12 weeks of therapy.

Results to week 72:

Twenty infants were enrolled from 16 clinical centres in five European countries. One child died at week 60 of non-HIV related causes. The triple antiretroviral combination with stavudine, didanosine and nelfinavir was well tolerated, associated with good clinical and immunologic outcomes but with high rate of virologic failure and emergence of resistance. At week 72, taking an intent-to-treat view by assignment to the original regimen, and excluding one infant who died (with HIV-1 RNA of < 50 copies/ml), only 5/19 (26%) infants achieved a durable viral suppression with HIV-1 RNA < 400 copies/ml [3].

Methods:

Children were followed up to three years, every three months and beyond 3 years every six months. The objective was to investigate clinical, virological and immunological long term response. Regarding statistical analysis, CD4 cell counts, height and weight were expressed as Z-scores with reference to healthy uninfected children. Proportions of children with HIV-1 RNA < 400 copies/ml were based on non-missing values. Changes in HIV-1 RNA, CD4 cells, height and weight Z-scores from baseline were assessed using the paired Wilcoxon signed-rank test. All reported P values are two sided.

Follow up and clinical findings:

Eighteen children achieved at least three years of follow-up. One child was lost to follow-up (on last available assessment at two years, the child was still on initial trial therapy with CD4% = 29% and HIV-1 RNA = 21,700 copies/ml). Median follow-up was 179 weeks (IQR 162-197). No AIDS events and no major toxicity occurred. No clinical lipodystrophy was reported.

Antiretroviral status at last assessment *(on 18 children)*:

At their last assessment, nine children (50 %) were still taking their initial therapy stavudine+didanosine+nelfinavir, although six of them were on virological failure by week 72. Of the **9** children who stopped the initial drugs regimen, **3** never restarted, while **6** switched immediately or subsequently to other regimens. Two children stopped permanently due to lack of virological response after 24 and 60 weeks of therapy respectively and one infant stopped at week 72 for parents request while HIV-1 RNA was < 50 copies/ml.
Out of the six who switched, **4** changed therapy before week 72 mainly due to viral load rebound or lack of viral load response. One child switched at week 168 due to high viral load. One child stopped at week 72 for parents request with an HIV-1 RNA < 50 copies/ml. There was an immediate viral load rebound > 5 log that remained high until the child switched to a new regimen at week 156. Details of all switches are given in Table 1.

Table 1 : Switches after first line therapy

Patient ID	**1st regimen stopped**	**HIV-1 RNA at switch (copies/ml)**	**Susbsequent regimen**	**Last HIV-1 RNA (copies/ml)**
1	Week 36	65,112	3TC+ABC+NVP	< 50 (week 180)
2	Week 60	> 500,000	3TC+Lop/r+NVP	< 50 (week 168)
3	Week 12	95,000 > 800,000 < 50 250,000	3TC+D4T+NFV ZDV+ABC+NVP+Lop/r ZDV+ABC+NVP None	 92,000 (week 192)
4	Week 36	1,480,000 315,000	3TC+D4T+ABC+RTV 3TC+D4T+ABC+Lop/r	 73 (week 192)
5	Week 168	158,886	DDI+Lop/r+EFV	206 (week 192)
6	Week 72	267,000	3TC+ABC+ Lop/r	< 50 (week 192)

HIV-1 RNA at week 156:

Seven children had HIV-1 RNA < 400 copies at 3 years. Four of them were on virological success after 72 weeks of therapy : 3 were still on initial therapy and 1 never restarted after week 72. The remaining 3 children had switched to other regimens prior to week 72. Among the 11 children who had HIV-1 RNA > 400 copies/ml at three years, 6 were still taking initial therapy with HIV-1 RNA ranging from 1824 to 19,000 copies/ml. The proportion of children with HIV-1 RNA < 400 copies/ml (7/18=39 %) was similar to that observed at week 72 (7/16=44%).

Immunology, height and weight at week 156:

Median CD4 % was 34 % (range 23-45), with the median increase from baseline in CD4 Z-score +0.42 (range –3.6 to 4.3, p=0.16). Weight and height adjusted for sex and age had increased significantly by 3 years (median increase Z-score from baseline + 0.99 and + 1.50

respectively, both P<=0.002). Changes from baseline in CD4 %, CD4 Z-score, weight and height for sex and age are summarized in Table 2.

Table 2. Change from baseline in CD4 percentage, CD4 z score, weight and height for sex and age

Week	Median (range) change in CD4% from baseline	Median (range) change in CD4 Z-score from baseline	Median (range) change in weight Z-score from baseline (*P**)	Median (range) change in height Z-score from baseline (P*)
12	+7 (-41 to 31)	+0.52 (-2.96 to 2.15)	+0.14 (-2.07 to 2.75) (*0.19*)	+0.28 (-1.19 to 1.98) (*0.117*)
24	+4 (-35 to 33)	+0.66 (-2.74 to 3.03)	+0.51 (-1.55 to 3.55) (*0.025*)	+0.83 (-1.06 to 3.52) (*0.004*)
72	-2 (-43 to 36)	+0.37 (-3.55 to 4.30)	+0.53 (-1.54 to 6.10) (*0.018*)	+1.41 (-1.10 to 6.85) (*0.001*)
156	1 (-36 to 34)	+0.42 (-3.58 to 4.30)	+0,99 (-0,61 to 6.63) *(0.002*)	1.50 (-0,71 to 8.56) (*0.001*)

* P value calculated with Wilcoxon signed-rank test

Conclusions:

In PENTA 7, children who started HAART early in life showed clinical and immunological improvement by 3 years. Initial regimen with stavudine+didanosine+nelfinavir was maintained in almost 50 % of children. Although some of them did not achieve viral load suppression, their HIV-1 RNA remained stable by three years. Switches due to poor virologic suppression were frequent and this can reduce the small pool of drugs available for children. Weight and height significantly increased by 3 years and immunological status remained stable or improved.

More potent antiretroviral drugs and more easily to administer are now available but progress in more suitable and palatable formulations for children is still needed. All these aspects could provide the support to treat infants during primary HIV infection but for how long ? Which other strategies (structured treatment interruption, vaccination, IL-2) must be undertaken in order to maintain immunological status and prevent long term toxicity ? Large cohorts of primary HIV infected children, treated or not and followed since birth, are indispensable to improve knowledge about infants antiretroviral response.

References

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Appendix

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