Difficulties in achieving suppression of viral replication in vertically HIV-1 infected infants early treated with d4T+ddI+NFV : The PENTA 7 Study

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Background

Many authors recommend starting early antiretroviral multitherapy for all infants aged less than 12 months as soon as an HIV confirmed diagnosis is established, regardless of clinical or immunological status or viral load. The rationale for early antiretroviral therapy in HIV infected infants < 3 months of age is supported by the presence of high viral load and the risk of rapid disease progression. However, only few data concerning this approach are available.

The PENTA 7 study was designed to assess toxicity, tolerability, efficacy and pharmacokinetics of triple therapy with d4T+ddI+Nelfinavir (NFV) in infants.

Objectives

The primary objective was to evaluate toxicity and tolerability of the triple therapy (d4T+ddI+NFV) in HIV–1 infected infants. Secondary objectives were to evaluate the impact of antiretroviral therapy (ART) in terms of changes in HIV-1 RNA, CD4 counts and clinical progression; the pharmacokinetics (PK) of NFV; the impact of ART on proviral DNA, intracellular RNA and Western Blot evolution; and the emergence of genotypic and phenotypic resistance.

Methods

PENTA 7 is a multicentre, phase I/II, open-label, non comparative study. 20 vertically HIV-1 infected children less than 12 weeks of age were enrolled over 1 year and treated with d4T suspension (2 mg/kg/d in 2 divided doses), ddI suspension (200mg/m^2/d in 2 divided doses) and NFV powder/crushed tablets (120 mg/kg/d TID and increased to 150 mg/kg/d BID after PK results showed low AUC's in the first 4 infants). Resistance testing at entry was required if the infant has been exposed in-utero to one or two of the study drugs. Regular clinical assessments and laboratory monitoring was performed to evaluate toxicity and efficacy. Plasma viral load was determined by RT-PCR quantification method using Amplicor HIV Monitor Roche performed in real time in a central Laboratory (Covance-Geneva). Nelfinavir PK studies have been performed at steady state (Week 2), at 6 months and at 18 months of age in children whose parents signed the relevant informed consent. Blood levels of NFV, d4T and ddI have been performed before dosing or, if not possible, at 1.5 or 3.5 hours (data not shown in this poster). Compliance was evaluated by parents/guardians self-completed questionnaire (data not shown)

Clinical failure was defined as the development of an AIDS event or death or new HIV related signs or symptoms of category B (CDC classification). Virological failure was defined as VL > 400 copies/ml after 24 weeks of therapy.

Results

Twenty children were enrolled from France (8), Germany (3), Italy (3), Spain (5) and UK (1). All children were followed for at least 48 weeks, median (range) follow-up was 75 weeks (48 -110).

I-BASELINE CHARACTERISTICS

Sex	Female	9
	Male	11
Ethnic origin	White	9
	Black African	9
	Black carribean	1
	Other	1
Age (mo)	<= 1	2
	- 2	3
	- 3	9
	> 3	6*
Mean (range)		2.6 (0.9 - 4.5)
Mean (range) weight		2.65 (0.65 - 3.62)
CDC stage at entry	N	12
	A	5
	B	3
Median (IQR) Log 10 HIV-1 RNA		5.51 (5.40 - 6.20)
Median (IQR) CD4 %		33 (24 - 46

* In days : 104, 105, 106, 110, 120, 137

Results

AT BIRTH		No of children median (range)
Mode of delivery	Vaginal	9
	Elective caesarean	7
	Emergency caesarean	4
Congenital abnormalities		None
Gestational age (in weeks)		37 (24 - 40)
Weight		2.98 (0.65 - 3.62)

II – ART RECEIVED TO REDUCE MATERNAL TRANSMISSION

Two children out of 20 did not receive any prophylaxis. Ten children were exposed in-utero to : AZT monotherapy (4), AZT+3TC (1) and multi-therapy including PI's or NVP (5). For 4 children we can assume that they were infected in-utero as the date of the evidence of infection was < 4 days from the date of birth.

III - TREATMENT

At time of analysis 13/20 patients remained on trial regimen. One patient died (see details below). Two children permanently discontinued at week 24 because of virological failure/poor compliance as evaluated by the clinician and 4 switched or stopped temporarily and then switched to other regimens for poor virological response.

IV - SAFETY

Death: I child (born prematurely at 30 weeks) died at week 60 due to a respiratory disease (obliterant bronchiolitis). The death was considered unrelated to HIV disease or trial drugs. At death the viral load was < 50 copies/ml

Four **serious adverse events (SAE)** have occurred: 2 hospitalisations, 1 neutropenia, 1 bronchiolitis. They were considered not to be related to treatment and were not followed by treatment modification.

Minor adverse events (MAE)(on trial treatment + 30 days). A total of 66 events in 15 children were reported by the clinicians. The most frequent minor adverse events were anaemia (10 in 5 children), raised ALK (7 in 6 children), raised AST/ALT (7 in 4 children), vomiting (5 in 4 children) and diarrhoea (3 in 3 children). Ten events were considered to be related to at least one of the trial drugs . However only two events led to trial drug modification (a short interruption of ddI/d4T/NFV after a rash/erythema in one child and a discontinuation of ddI due to diarrhoea in a second child).

V-EFFICACY

Efficacy analyses were undertaken ignoring treatment changes (intention to treat).

Clinical progression

Two children changed CDC stage : A to B at week 8 and N to A at week 20.

Effect of Treatment on Plasma HIV-1 RNA

A rapid decrease of the plasma HIV-1 RNA occurred after 4 weeks of therapy (median drop of 2 log) but this decline was not sustained beyond week 12. Median (Interquartile range) viral load reduction from baseline was **–2.05 (-3.39 to –1.06)** $\log_{10}$ copies/mL and **–1.96 (-3.41 to –0.99)** respectively at week 24 and week 48 (See Figure 1).

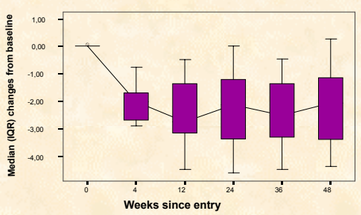

Figure 1. HIV-1 RNA median changes from baseline

The proportions of children with plasma HIV-1 RNA < 400 copies/mL and < 50 copies/mL are given in table 2. After 48 weeks of follow-up, **38.9 %** children were under 400 copies/mL (**22.2 %** under 50 copies/mL).

Week	N	N (%) < 400	N (%) < 50
4	18	2 (11.1)	0 (0)
12	19	6 (31.6)	2 (10.5)
24	20	8 (40)	4 (20)
36	16	7 (43.8)	4 (25)
48	18	7 (38.9)	4 (22.2)

Table 2. Proportion with HIV-1 RNA < 50/400 cp/mL

Effect of Treatment on CD4 cells

The CD4 cell count and the CD4 percentage had increased from baseline at W24 and W48. The median increases of CD4 % were 5% at W24 and 1% at W48. The median change in CD4 Z score was 0.74 at 24 weeks and 0.30 at 48 weeks. The differences from baseline were not statistically significant. In all children the CD4 % remained > 20 % throughout.

VI - RESISTANCE

Samples and Methods

- Genotypic resistance test was performed at baseline in all children and on the last sample available from children failing therapy (> 400 copies/ml on 2 consecutive viral load measures) after 12 weeks of therapy.
- Reverse transcriptase and protease genes were sequenced using the Consensus technique of the ANRS Antiretroviral Study Group (in-house technique**).**

Resistance results

- Two of 20 children had resistance mutations at baseline.
- For 6 children, the viral load was controlled during the follow up (until W36 to W72).
- For 9 children, there was no acquisition of resistance mutations despite high viral load.
- For 5 children, we demonstrated an acquisition of resistance mutations to treatment (3 to Nelfinavir, 1 to d4T + Nelfinavir, 1 to ddI).

Resistance data for children with uncontrolled viral load and acquisition of resistance mutations to treatment

PATIENT	DATE	RT mutations	Protease mutations
GI002001	W0	No mutation	L63P
	W12	No mutation	D30D/N, L63P, N88N/S
	W24	No mutation	D30N, L63P
	W48	No mutation	D30N, M36I, L63P
GD004001	W0	No mutation	M36I, V82I
	W72	No mutation	M36I, V77I, V82I, N88S
GE005002	W0	No mutation	L63P
	W24	T215Y	D30N, M36I, L63P
	W48	T215Y	D30N, M36I, L63P, N88D
GE006001	W24	No mutation	L63P
	W48	L74V	L63P
GF 001001	W0	No mutation	L10V, M36I, L63P
(Switch D4T, 3TC, NFV at W12)	W32	M184V	D30N, M36I, L63P

Discussion

Despite good short term tolerance and clinical and immunological stability, more than half of the infants had detectable viral load (VL> 400 copies/ml) and 5/14 (36%) had evidence of genotypic resistance.

In accordance with other studies, we showed that tolerance of multitherapy in infants was good and no severe adverse events related to the treatment occurred. However longer follow-up will be required to detect long-term toxicity. Despite the lack of abnormalities of lipids or glycemias we should be cautious concerning the risk of long term onset of lipodystrophy abnormalities or cardiovascular risk factors in these infants. We did not observe major clinical progression, in particular no encephalopathy. No infant had CD4 % less than 20% at week 48. These results are encouraging but the small number of children in this non comparative study does not allow any conclusions to be drawn about the clinical or immunological benefit of early treatment. One of the main concerns is the occurrence of 14 children with virological failure which was associated with genotypic resistance in 5 infants. Virological failures seem more frequent in our study than in adults treated for primary infection where undetectable viral load is achieved in about 80% of patients. Some paediatric studies have reported better results in infants. Luzuriaga et al reported virological suppression in 15 of 24 children (62%) treated with early HAART. Several issues can explain virological failure in our study: firstly, high baseline viral load in infants could be a barrier to achieving undetectable viral load in infants; secondly, adherence of mothers of asymptomatic infants may be less good; also obtaining adequate pharmacokinetic levels of Nelfinavir appears to be very difficult. Quadruple therapy could be more appropriate for infants with very high viral load but such a regimen may also be more complicated in practice because of the difficulties of administration and drug interactions. We investigated the relationship between baseline variables and virological failure at week 24. Baseline HIV-1 RNA, CD4 %, Z score for weight, ethnic origin were found to be non significant. However, the primary viral load response at week 4 was found to be statistically significant (Mann-Whitney, non-parametric test, p=0.027).

The pharmacokinetics of NFV is one of the main issues. We have previously shown, in accordance with Caparelli et al, that NFV doses should be increased from 120 to 150 mg/kg/day in infants. Analysis of blood levels as children get older are ongoing. All infants have switched to NFV tablets due to the difficulties in administration of powder. These difficulties were reported in a self questionnaire (data not shown). Underexposure to NFV could lead to persistent viral replication and emergence of genotypic resistance.

In conclusion, we observed in our study of early treatment with d4T+ddI+NFV in infants a high rate of virological failure and HIV genotypic resistance. However, the study population is too small to draw general conclusions. A major effort is required to improve compliance and determine appropriate doses of protease inhibitors so as to optimise antiretroviral treatment and virological response.

Participants

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