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Treatment interruption in children with chronic HIV-infection: the results of the paediatric European network for treatment of AIDS (PENTA 11) trial

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Background/Objectives

Compared to adults, in vertically HIV-infected children:

- Antiretroviral treatment (ART) is often started early due to higher risks of clinical progression and poor predictive value of CD4 for disease progression. Children will be on ART for much longer than adults:
  - greater potential for long-term drug toxicity, and children are more likely to interrupt ART (especially adolescents).
- Children often have poorer virological response due to limited treatment options, formularies, variable PK and adherence issues:
  - increased potential to develop resistance.
- However children tend to have good immunological response due to an active thymus and predominantly CD45RA+ naive cells.

For these reasons children may respond differently to interruptions in ART compared to adults.

The specific objectives of PENTA 11 were:

- To determine whether children with chronic HIV infection undergoing planned antiretroviral (ART) treatment interruptions are disadvantaged clinically, immunologically or virologically by periods of time off ART.
- To assess HIV-specific immune responses during and after interruptions of ART compared with continuous ART, in an immunology/virology substudy (ongoing).
- To assess the pharmacokinetics of agents with long half-lives – NNRTI and lamivudine and their association with the development of resistance in the context of planned treatment interruptions (published [1]).

Trial design

Trial design and participants

PENTA 11 was a multi-centre randomised open phase II exploratory clinical trial evaluating the role of planned treatment interruptions (PTIs) in the management of HIV infected children who have responded well to ART.

HIV- infected children aged 2 to 15 years old, on any ART regimen containing 3 or more drugs which they had taken for at least 24 weeks, and met CD4 and HIV-1 RNA criteria as shown in Figure1 were randomised to:

- Continuous ART (CT): continue to their current regimen
- Planned Treatment Interruptions (PTI): strategy of CD4-guided PTIs

After SMART results were released in 2006 and the data safety monitoring committee reviewed trial data and all available adult trial results, and increased safety measures were added:

- maximum time off ART 48 weeks
- minimum time on ART before stopping again 24 weeks
- children who had to restart within the first 10 weeks due to falling CD4 were not allowed to do further PTIs.

72 weeks minimum follow-up was completed by end of May 2008.

Trial endpoints

The primary endpoint was any of:

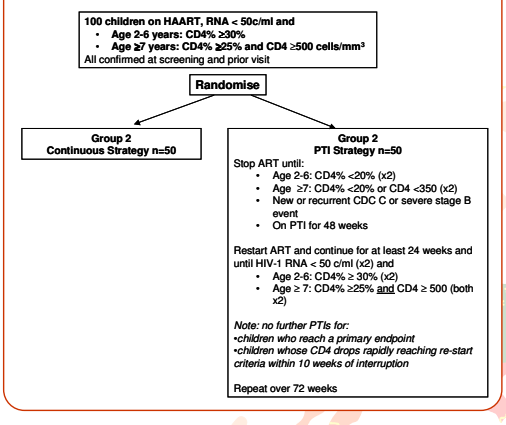
- CD4% <15% (age 2-6)
- CD4% <15% and CD4<200 cells/mm^3 (age ≥7)
- new CDC stage C diagnosis
- death

Secondary endpoints included changes in ART, ART-related toxicity, resistance, and adherence and acceptability.

Sample size

The aim was to enrol 100 children, 50 per group. Assuming no children in the CT group experience a primary endpoint, 50 children per group provided 80% power to exclude an increase in event rates of more than 15% (to 15%) in the PTI group (two-sided alpha = 0.05).

Figure 1: schematic diagram of the design of PENTA 11



Baseline characteristics

Baseline characteristics were well balanced in the two groups (Table 1)

Table 1: Baseline characteristics

	CT	PTI	Total
Children randomised and included	53	56	109
Sex: male	22 (42%)	27 (48%)	49 (45%)
Age (years): median [range]	9.9 [2.2,15.1]	9.0 [3.5,15.9]	9.3 [2.2,15.9]
Ethnic origin: % white / black / asian / other	32 / 32 / 23 / 13	37 / 30 / 20 / 12	35 / 31 / 21 / 13
CDC Stage % NorA / B / C	40 / 26 / 34	54 / 29 / 18	47 / 27 / 26
CD4%: median [IQR]	37 [34,40]	37 [33,42]	37 [33,41]
CD4 (cells/mm^3):median [IQR]	965 [741,1222]	967 [844,1302]	966 [793,1258]
Nadir CD4%*: median [IQR]	18 [9,28]	19 [11,25]	18 [10,27]
Number of classes exposed to:			
All 3 classes	19 (36%)	14 (25%)	33 (30%)
NRTIs + PIs only	11 (21%)	17 (30%)	28 (26%)
NRTIs + NNRTIs only	22 (42%)	25 (45%)	47 (43%)
NRTIs only	1 (2%)	0 (0%)	1 (1%)
Previous mono/dual ART	18 (34%)	15 (27%)	33 (30%)
ART exposure (years): median [IQR]	6.6 [3.9,8.9]	5.6 [3.2,8.3]	5.7 [3.4,8.7]
No. of drugs received: median [IQR]	4.0 [3.0,6.0]	4.0 [3.0,6.0]	4.0 [3.0,6.0]

* missing for 11 children (6 CT, 5 PTI), column percentages are of non-missing values.

Follow-up and ART received

After a median follow-up of 130 weeks (2.5 years) (range 30 to 180 weeks; 1 child lost to follow-up), 4% of time was spent off ART in the CT group compared to 48% in the PTI group.

After the 1st PTI, 14 (25%) children restarted ART for falling CD4%/count before 48 weeks (9 restarted within 10 weeks of stopping), 32 (57%) restarted after 48 weeks off ART and 7 (12%) restarted for non-protocol reasons. 16 children stopped ART for a 2nd PTI.

Although 38% of children restarting ART after 1st PTI did not restart the same regimen they had stopped (due to simplification, switching from stavudine and nelfinavir), there was no of a difference in the number or type of ART drugs prescribed between the groups.

Primary endpoint

No child died or had a CDC C event

Children with a CD4 endpoint:

CD4% <15% (2-6yr): 0 CT vs 3 PTI

CD4% <15% and CD4<200 (≥7yr): 1 CT vs 1 PT

Total primary endpoints:

1 (2%) CT vs 4 (7%) (difference 5%, 95% CI (-2%, 13%), p=0.2)

Clinical and laboratory

Clinical events: Although the rate of clinical events in the PTI group was approximately twice that in the CT group, most events were minor (Table 2). Excess events in the PTI group were lymphadenopathy, a variety of skin complaints and mild CNS events (headaches), and approximately one third occurred while children were on ART. The number of infections in each arm was similar.

As PENTA 11 was an open study, the excess events in the PTI group could have been because doctors and families were more concerned and looked more carefully at children in the PTI group than the CT group.

Laboratory events: There was no evidence of a difference in the rate of laboratory events between groups.

Hospitalisations: There were 18 admissions to hospital (5 CT, 13 PTI) for 16 children (5 CT, 11 PTI). Most admissions were for 1 or 2 days (1 CT,8 PTI). Four children were admitted for more than a week (3CT, 1 PTI).

Table 2: Clinical events

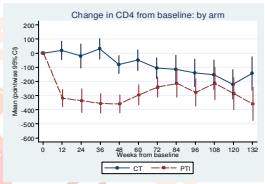
	CT	PTI	Total
Total events	**26**	**50**	**RR 2.4**
Total children	**15**	**29**	**(1.3, 4.4)**
Event rate /100 child-yrs (95% CI)	**16 (10-27)**	**38 (26-54)**	**p=0.004**
CDC B events: Osteomyelitis	0	1	1
Blood/lymphatic system:	0	10	10
Mainly Lymphadenopathy	0	7	
Thrombocytopenia	0	1	
Skin / subcutaneous tissue	3	9	12
(mainly rash)			
Henoch-Schonlein purpura	0	1	
Lipodystrophy	1	0	
CNS/Psychiatric:	1	7	8
(mainly headache)			
Facial palsy	0	1	
Gastrointestinal disorders	4	6	10
Infections (mainly viral respiratory)	15	12	27
Respiratory	3	2	5

Immunology

Over total follow-up, 98% CT vs 96% PTI of child-years were spent with CD4 count ≥ 350 cells/mm^3.

Mean CD4 count change from 0-72 weeks (Figure 2) in CT vs PTI was -106 CT vs -240 PTI cells/mm^3 (diff. -134 95% CI (-234,-31) p=0.01). But 6 children were off ART in PTI at 72 weeks; mean CD4 change 0-72 weeks was -124 cells/mm^3 in 27 PTI children back on ART for ≥24 wks.

Figure 2: Changes in CD4 from baseline



CD4 recovery: Mean (SE) CD4 z-score 24 weeks after restarting after 1st PTI, compared to baseline was -0.1 (0.3), -0.9 (0.2) and -1.3 (0.3) in children aged ≥2 to <7, ≥7 to <11, and ≥11 years respectively in the PTI arm (p=0.02), suggesting that age adjusted CD4 recovery may be better in younger children.

Virology

The proportion of children with HIV-1 RNA <400 copies/ml and <50 copies/ml at 72 weeks was higher in the PTI group (Figure 3):

VL <400 c/ml: 94% CT vs 81% PTI (diff. 13% (95% CI 1%,26%) p=0.05)

VL <50 c/ml: 85% CT vs 58% PTI (diff. 27% (95% CI 11%,44% p=0.003).

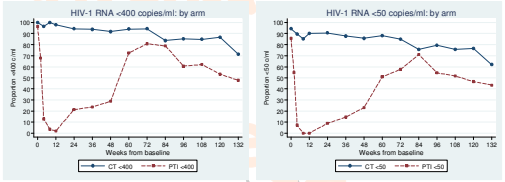
In exploratory analysis, for 28 children in the PTI group on ART for at least 24 weeks at week 72, 89% were <400 c/ml and 68% <50 c/ml.

Of the 30 children with HIV-1 RNA ≥50 copies/ml at 72 weeks, 8 were off ART (2CT, 6PTI), 7 were blips (4 CT, 3 PTI), 6 had decreasing HIV-1 RNA after restarting ART (0 CT, 6 PTI) and 9 were rebounds (2 CT, 7 PTI).

Resistance: Of 13 children (7 CT, 6 PTI) with viral rebound (2 consecutive HIV-1 RNA >100 copies/ml) and a resistance test available, 10 had resistance (5 CT, 5 PTI) mutations; 6 had four or more mutations (4 CT, 2 PTI). Preliminary analysis suggests that adherence to ART after a PTI may have been inadequate in at least 3 children in the PTI group; resistance in other children was likely related to previous mono/dual ART.

23 of 68 samples from 19 PTI children had resistance after stopping or restarting ART. For 22 samples resistance was associated with previous drug exposure and virological failure. One new 103N mutation developed in a child on efavirenz with detectable drug levels 2 weeks after stopping; the protocol was subsequently changed to advocate replacement for 4 weeks and not stagger stop with efavirenz.

Figure 3: % of children with HIV-RNA <400/<50 c/ml at week 72



Summary & Conclusion

Summary: In this pilot paediatric trial of CD4-guided PTI in chronic HIV:

- Children in the PTI group spent ~50% time off ART
- No deaths or serious clinical events; there were more minor clinical events (but not infections) in the PTI group
- Despite relatively advanced disease before starting ART:
  - ~60% children only restarted ART because they reached 48 weeks;
  - only 4% time spent with CD4 <350 cells/mm3
- Although CD4 levels and HIV RNA suppression were inferior at 72 weeks in the PTI group, some PTI children were off ART at 72 weeks
- CD4 recovery after PTI was significantly better in younger children
- No evidence increase in resistance in PTI children

Next steps:

- Further analyses – lipids, adherence and acceptability
- Substudies – detailed immunology/virology, PK after 2nd PTI
- Annual follow-up of all children in PENTA 11 for 5 years:
  - Immunological/virological recovery and neurocognitive function

Conclusion:

- Because PENTA 11 was a small, pilot study and not formally powered to detect differences, we cannot currently recommend children undergo CD4 guided PTIs.
- PENTA 11 results so far provide useful information for carers/children who may anyway interrupt ART and reassurance for ongoing paediatric trials: BANA trial – CD4-driven treatment interruptions (600 children in Botswana) CHER trial - Early limited ART after primary infection in infants
- Balance of risks and benefits of lifelong ART and HIV is different in vertically HIV-infected children vs adults. The aim is to ensure children move to adulthood with no adverse clinical outcomes, good growth and CD4 and minimal resistance.

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