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Neurocognitive and Quality of Life Outcomes in Children after Planned Treatment Interruptions: the randomized PENTA 11 trial

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Introduction

Families and health providers are interested in all aspects of child's progress and how health and HIV may affect performance in everyday tasks. CNS abnormalities, in particular deficits in attention, executive functions and processing speed are increasingly being reported in perinatally-acquired HIV-infected children. Similarly, quality of life (QoL) assessments has become of utmost importance in the follow-up of children and adolescent with chronic diseases. There are few longitudinal or comparison studies on cognitive-learning outcomes and QoL in HIV-infected children. Although HAART may improve neurocognitive function, there are concerns about long term outcomes. Neurodevelopmental functions and QoL were compared in the ongoing long-term follow-up (LTFU) of children in the PENTA 11 trial that is planned up to 5 years since randomization of the main trial (AIDS 2010;24: 231-41). PENTA 11 was a randomized trial of CD4-guided Planned Treatment Interruptions (PTIs) compared with continuous therapy (CT) in children aged 2-15 years on stable ART. After 130 weeks (48% time off ART in the PTI group), no major clinical/immunological differences were observed between PTI and CT. At LTFU visits (2009 & 2010, children in PTI were back on ART), no significant clinical, CD4 or VL differences were found in PTI vs CT. At these visits, 3 subscales of the WISC IV intelligence scale and self report and carer versions of PedsQL quality of life were administered.

Patients and methods

- Measures chosen to assess IQ and QoL had to be appropriate to age range of population (mainly school aged), with tests easily available in countries included in PENTA 11, and also administered in standardised way and in relatively short time
- PENTA 11 trial has been extended (year 1 and 2) to include a IQ measure (WASE: Wechsler Abbreviated Scale of Intelligence)
- The decision to include these measures made after completion of PENTA 11 trial (so NO pre trial baseline data were available). Collected data at year 1 and year 2 follow-up during 2009 and 2010.
- Variables analysed for factors associated with lower scale scores included age, CDC category, CD4 nadir (< 15% and < 200 CD4), Gender, Ethnicity, Country of assessment. Means for each scale were compared using linear regression (WISC subtests) and robust regression (PedsQL dimensions). Models were adjusted for stratifying factors as in the main trial (age <7/≥7 years), pre-HAART nadir CD4 (<15%/≥15%) or HAART started before 5 months.

Neuropsychological assessment
 3 subscales of WISC IV or III (Wechsler Intelligence Scale for Children)
 *Coding: Copying symbols attached to numbers within time limit
 *Functions: *Processing speed & sustained attention*
 *Symbol Search: Scanning for presence or absence of presented shapes from a sequence (within time limit)
 *Functions: *Information processing (also requires sustained attention)*
 *Digit Span: Repeating strings of presented numbers which increase in length (forwards and backwards)
 *Functions: *short term memory (backwards requires ability to abstract information)*
 *Score < 7 on any subscales is the cut-off for clinical concern.
 *Not available on WISC III

Quality of life assessment: PedsQL:
 (Paediatric Health Related Quality of Life Inventory)
 - 23 items each with 5 point Likert scale Carer and Child Scales.
 Scales for young child, school age, teenagers and young adult ages.
 PedsQL is being used for a variety of other paediatric chronic illnesses (diabetes, sickle cell, cancer, rheumatology)
 4 subscales: Physical, Emotional, Social & School Functions
 General Psychosocial Index (Combination of Emotional, Social and School functions).
 Score between 0 and 100 (100= no concerns)
 Score < 70 on any scale is the cut-off for clinical concern

Objectives

- To see if there are any significant differences between children's IQ and QoL in CT and PTI arms
- To assess the IQ and QoL overall at year 1 and 2 after randomization
- To look for relationships between the 3 different WISC subscales on general cognitive level and 4 scales on QoL
- To determine possible factors associated with lower scales scores

Baseline characteristics at randomization in PENTA 11

	CT	PTI
Total		
Mean age (y.) (IQR: 6.3-11.6)	9.9	9.0
Male (%)	42	48
Ethnic origin (% white)	32	37
CDC stage C (%)	34	18
CD4 % (IQR: 33-41)	37	37
CD4 cell count (793-1258)	965	967
Age at ART start (0.5-5.1)	2.2	2.1
On ART at randomization	2.2	2.2
On ART at year 1	43	46
On ART at year 2	43	46

- Possible factors associated with lower scales scores**
- More emotional difficulties reported in female group (p < 0.05)
 - Boys slightly poorer scores than girls in WISC coding subscale (p < 0.05)
 - Older children poorer digit span WISC subscale (p < 0.05)
 - Ethnicity – complex results. Effects of whether child moved from one country to another not racial background
 - Low nadir CD4 associated with reports of poorer outcomes: WISC (Digit span subscale) and PedsQL (p < 0.05)

Limitations of the study

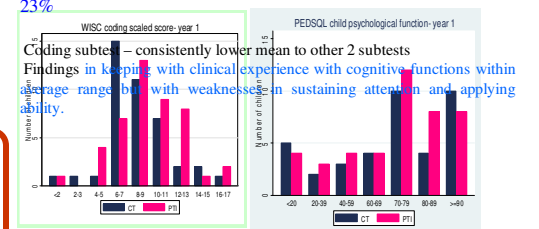
- No baseline evaluations
- Randomized trial sample size
- Short term follow up
- Tests not sensitive enough to pick up small differences or subtle neurocognitive and QoL abnormalities

RESULTS

Neurocognitive findings from whole population (CT and PTI combined)

WISC IV: 3 subscales of WISC IV (Wechsler Intelligence Scale for Children)

Children		Symbol search		Coding		Digit
		CT	PTI	CT	PTI	
Span	Year 1 n=89	8.9	9.6	8.3	9.2	9.2
	Mean					
SD	Year 1 n=89	2.9	3.0	3.0	3.2	3.2
	Mean					
Diff (95%CI)	Year 1 n=89	0.6	(-0.7,1.9)	-0.5	(-1.8,0.8)	0.7 (-0.7,2.1)
	p:	0.4		0.44		0.32
Year 2 n=86	PTI	9.8	9.3	8.6	9.0	9.3
	Mean					
SD	Year 2 n=86	3.1	2.5	3.0	2.8	2.8
	Mean					
Diff (95%CI)	Year 2 n=86	-0.5	(-1.8,0.8)	0.5	(-0.8,1.7)	0.6 (-0.7,1.9)
	p:	0.4		0.48		0.36



Conclusions

- After 1 and 2 years back on ART, children in the PTI arm of PENTA 11 had similar group scores on neurocognitive functions and quality of life measures compared with those remaining on CT.
- However a significant proportion of children in both arms had low scores on WISC subtests and PedsQL measures.
- Continue follow-up for the full 5 years is scheduled in the current protocol. Inclusion of neuro-cognitive and QoL measures in ongoing

PedsQL findings

Child Report (school age 5-18yrs)

Scale	Mean		% score < 70 (clinical concern)		yr 2
	yr 1 (n=89)	yr2(n= 86)	yr 1	yr 2	
Combined					
Physical	82.9	86.0	13.6%	13.9%	20 %
Emotional	74.9	74.3	33.3%	27.8%	43 %
Social	85.7	87.7	14.8%	10.1%	21 %
School	71.4	73.7	38.3%	32.9%	52 %

School functioning and Emotional scales consistently lower than physical and social scales (both child and carer reports)
 Similar to findings from other chronic childhood illnesses
 No group differences were observed on any PedsQL dimensions comparing PTI vs CT
 Data suggest that emotional and school functioning reciprocally affect each other.

Parents Report

Scale	Mean		% scoring < 70 (clinical concern)		yr 2
	yr1(n=89)	yr2(n= 86)	yr 1	yr 2	
Combined					
Physical	78.1	81.0	30.1%	24%	41 %
Emotional	70.7	71.1	38.6%	40%	51 %
Social	78.3	80.7	26.5%	19.7%	19.7%
School	65.1	68.6	36%	50%	42.7%

* Profile consistent with that from Child report
 * School functioning and Emotional scales consistently lower than physical and social scales (both child and carer reports)

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