



Neurocognitive Impairment in a Romanian Cohort of Children and Young Adults Infected with HIV-1 Clade F

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Background

Romanian cohort:

- Young adults: 18 - 22 y.o.
- Clade F-1, horizontally acquired during the first years of life
- Homogeneous population, balanced M/F ratio
- Currently there are around 8000 survivors out of estimated 14,000 infected between 1987-1990
- On HAART since 1999

Cognitive impairment in HIV-1 infected children

- Age-dependent neurologic presentation of HIV-infection
- Lack of definition for cognitive impairment and clinical data in older children ¹
- HIV+ children have impaired psycho-motor development even in the absence of AIDS defining diseases
- Adolescents with AIDS have symptoms similar to adults (dementia, bradikinezia and spasticity) ²

¹. Angelini L (2000). Neurological Sciences 21 (3): 135-142

² Mitchell, W. (2001). Ment Retard Dev Disabil Res Rev 7(3): 211-6.

Objectives

- Retrospective evaluation (1996-2007) of particular features of HIV encephalopathy (HIVE) in children and adolescents with parenterally transmitted HIV-infection
- Prospective evaluation (2007 – 2008) on a group of HIV-1 infected adolescents based on the current HIV Associated Neurocognitive Disorder (HAND) criteria.

Methods

- Neurological exam
- Psychological evaluation with age-adjusted standardized methods:
 - Wechsler Intelligence Scale for Children, 3rd. ed. (WISC-III) 1991 –Aug 1996- Mar 1999
 - HIV Neurocognitive Research Center (HNRC) battery of tests

Results

- 110 children/adolescents with HIV
- 20.1% (highest prevalence) of AIDS defining diseases

Yearly distribution of patients with HIVE and AIDS defining diseases



- preHAART period - 61 HIVE out of 287 AIDS defining diseases, 21.3%
- HAART period - 49 HIVE out of 260 AIDS defining diseases, 18.8% (p=ns)

General characteristics of children with HIV

Girls/boys		34/76
Community	Urban/Rural	55/41
	Institutions	14
HIV transmission route	Parenteral	95
	Vertical	5
	Unknown	10
Mean age at HIV diagnosis		11.1± 3.7 years
CDC clinical classification before dg HIV	A	5 pts.
	B	88 pts.
	C	17 pts.
Immunological status at HIV diagnosis	Median CD4	64 lf/mm³ (limits 0-402 lf/mm ³)
Pts on stable ART > 6 months before HIV (with good adherence)	ART	9 pts.
	HAART	11 pts.
Pts without stable ART before HIV	Newly diagnosed with HIV	20
	Failure/non-adherence	34
	ART < 6 months	11
	Never treated	25

Clinical diagnosis criteria

Hyperreflexia 45.5%

Pyramidal syndrome 39.1%

Cerebellar syndrome 37.3%

Behavioral disorders 24.5 %

Cognitive deficit 68.1%

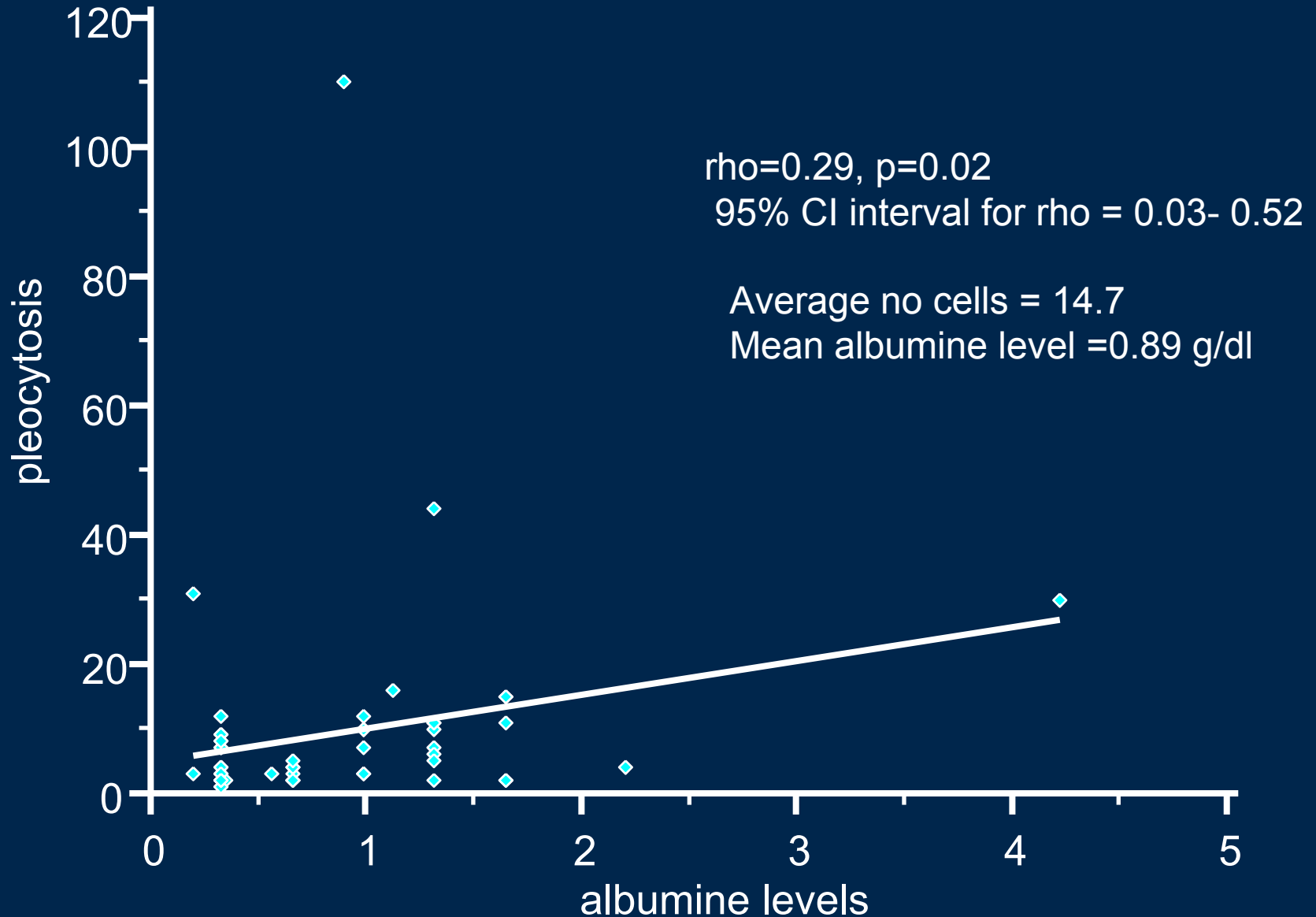
➤memory

➤20%

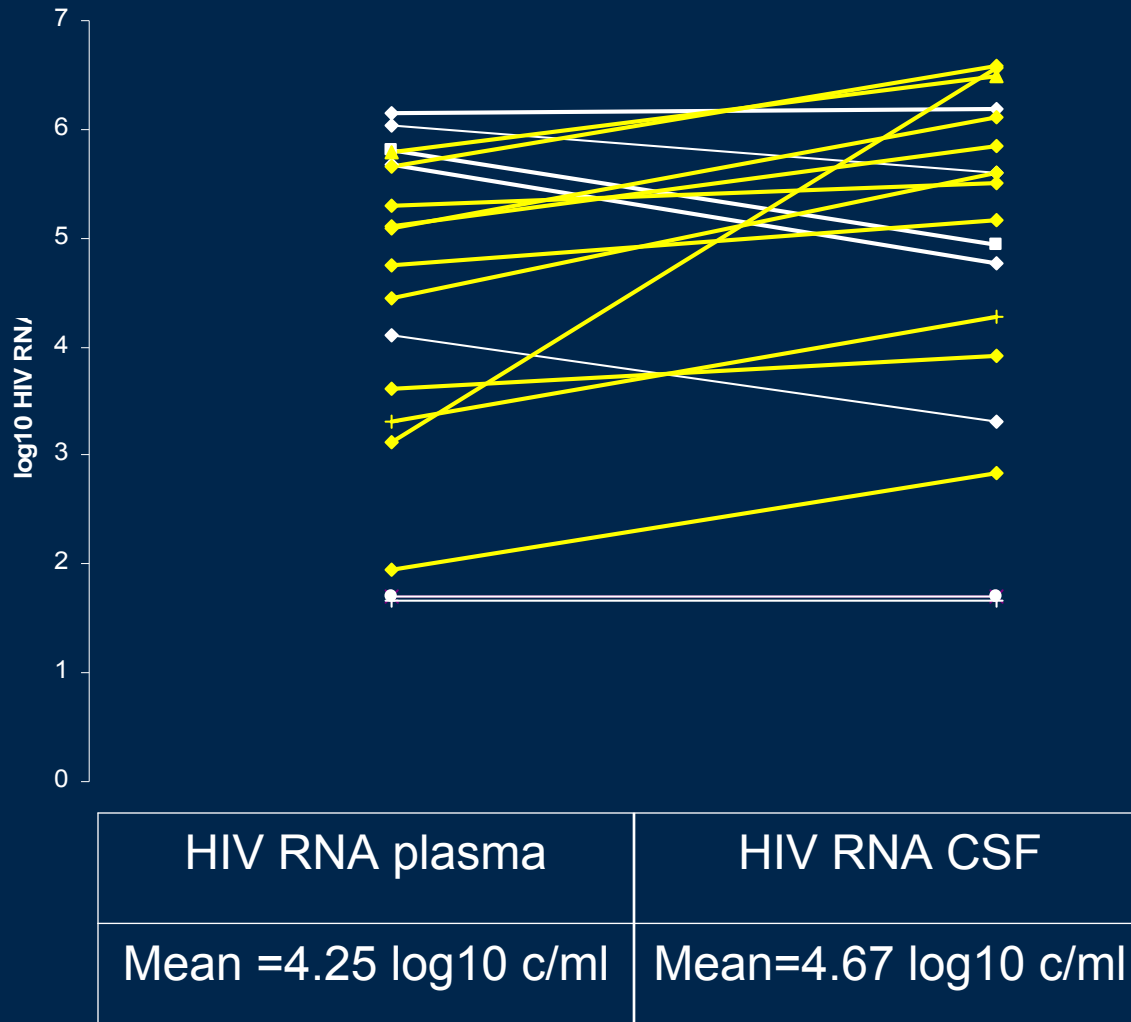
➤reduced performances

➤41.8%

Correlation between pleocytosis and albumin levels



Paired plasma-CSF HIV RNA values in a subgroup of 19 adolescents with HIV



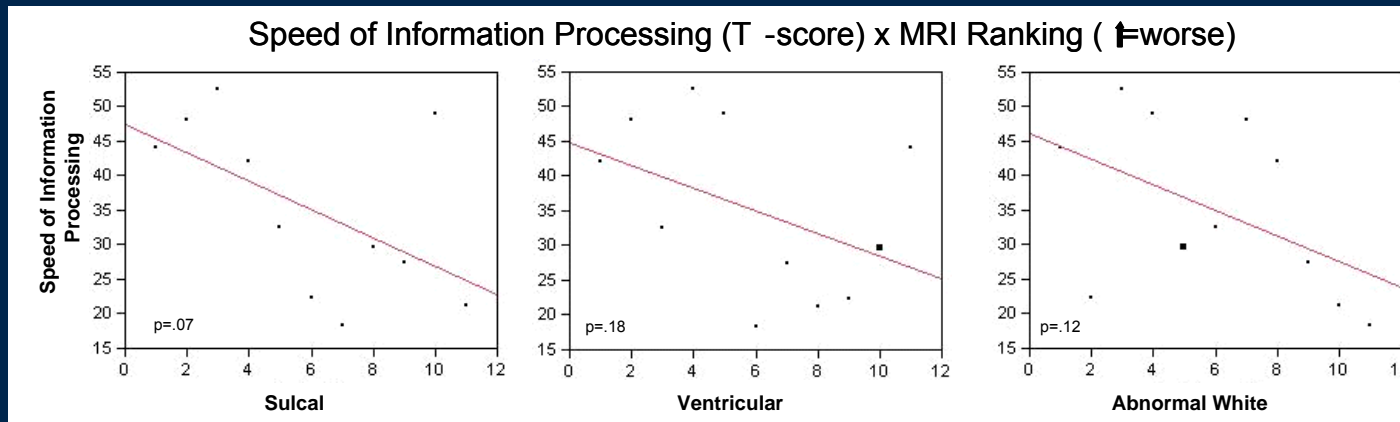
12 of 19 patients with HIV and paired plasma-CSF samples had higher CSF HIV RNA levels compared to plasma (5.42 ± 1.18 log₁₀ c/ml vs. 4.51 ± 1.26 log₁₀ c/ml, $p < 0.05$)

Neuroimaging studies

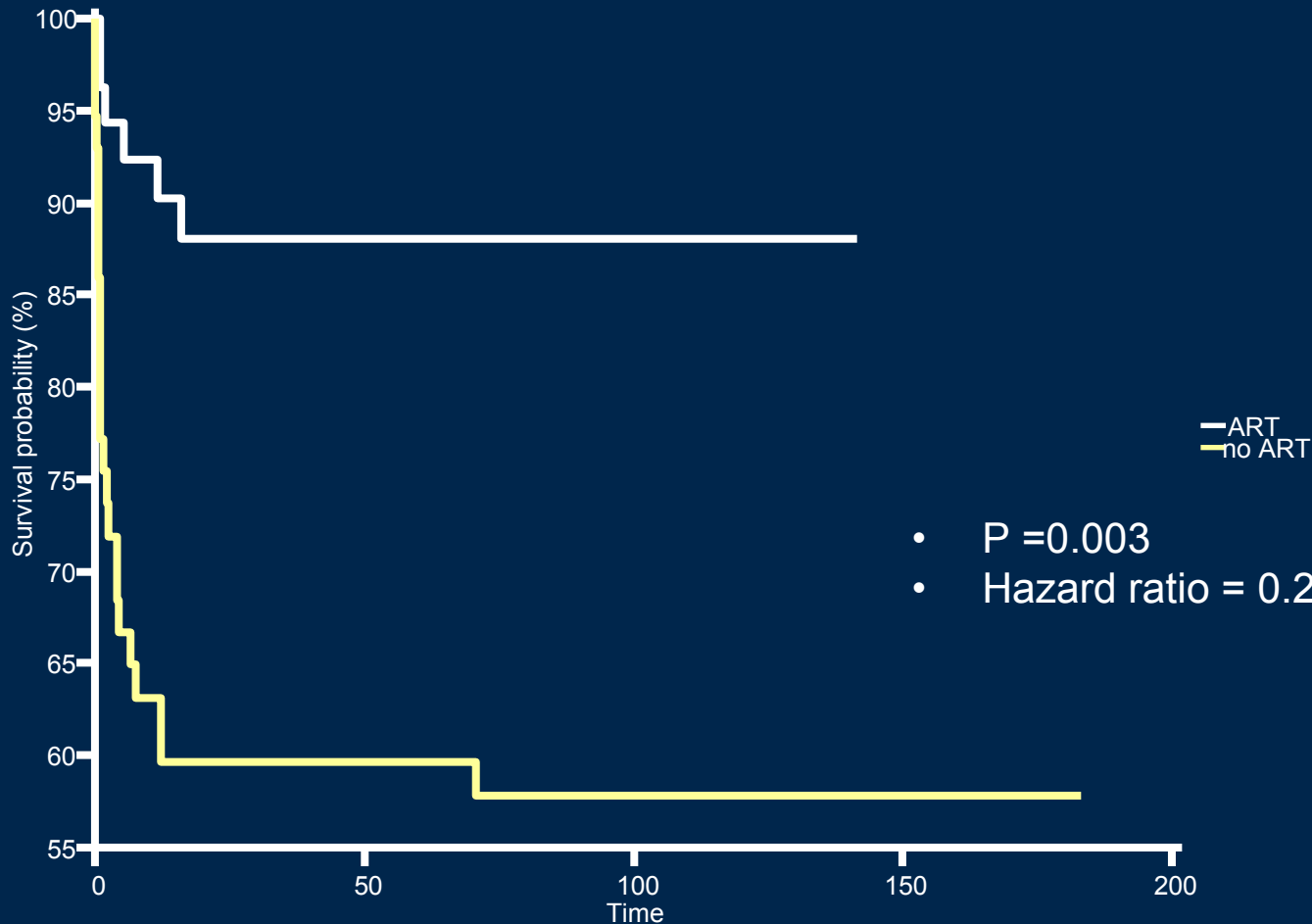
- Main findings:
 - cortical & subcortical atrophy 84.6% (55 of 65 pts)
 - MRI demyelinating lesions 66 %
 - Positive correlation between MRI rankings and brain performances

Analysis of the association between T scores and MRI rankings.

Higher values represent lower performance and more brain abnormalities.



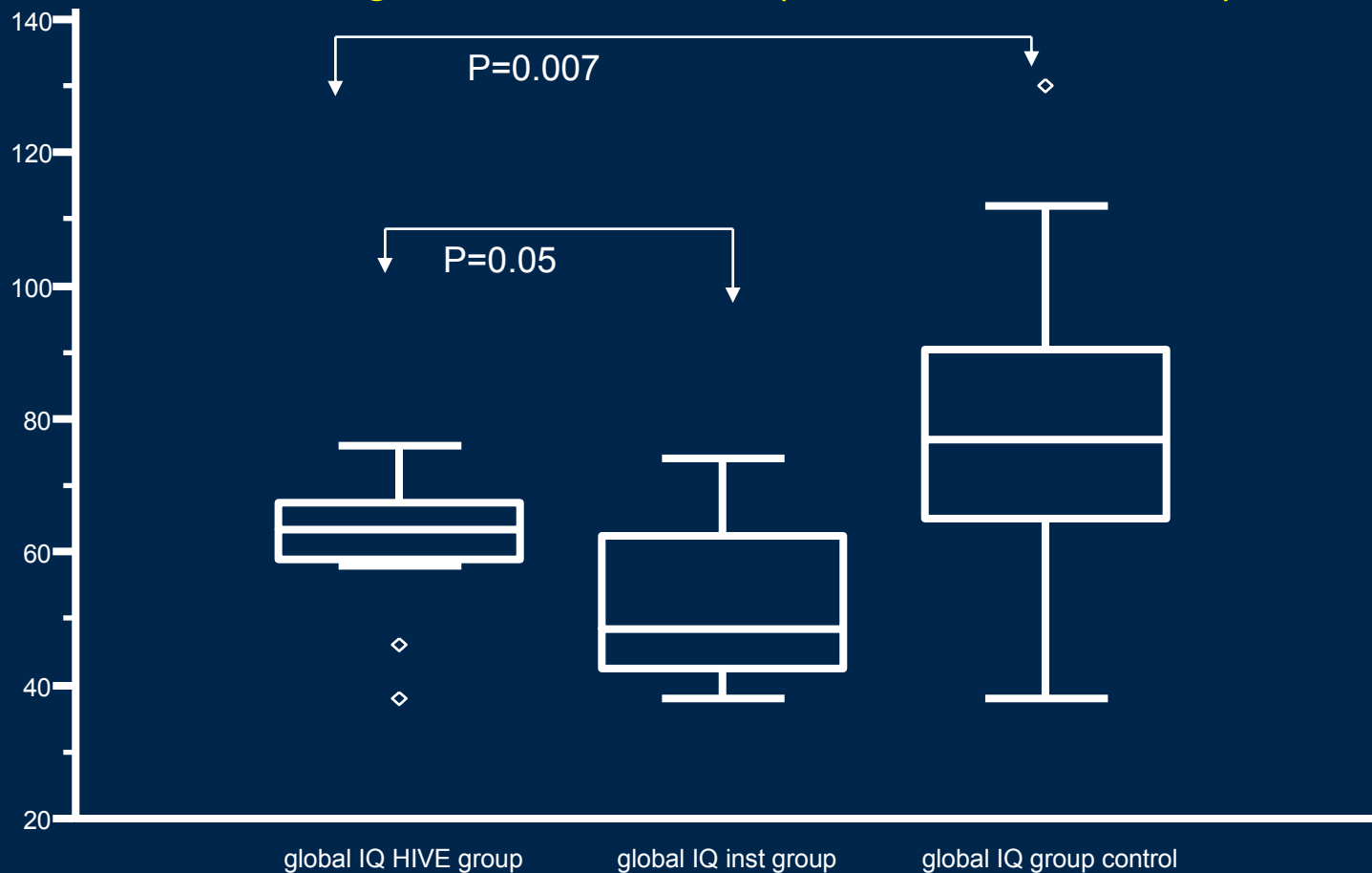
Mortality in children with HIV



- P = 0.003
- Hazard ratio = 0.26 (95% CI 0.12-0.54)

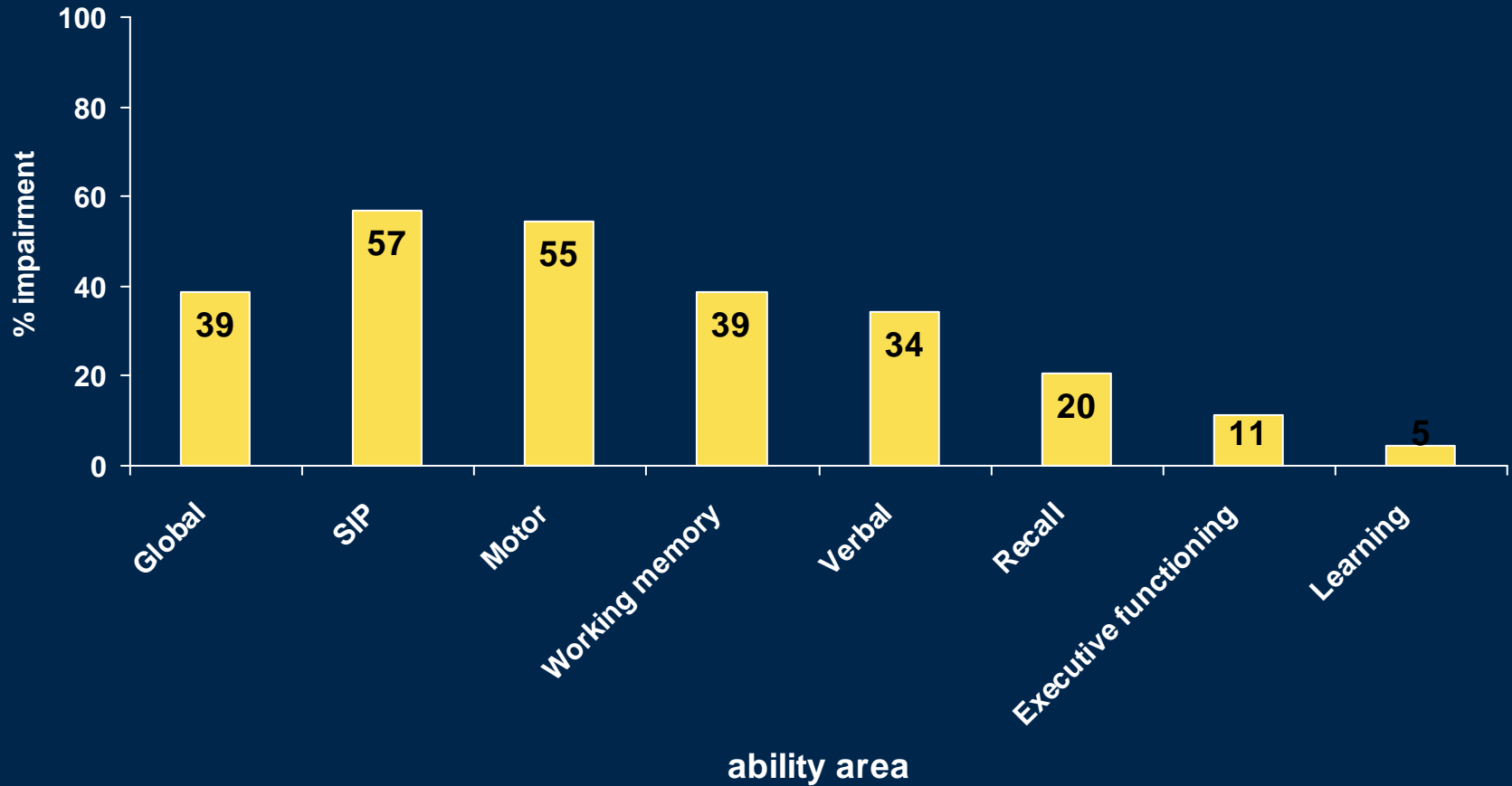
- The overall mortality rate was 27.3%,
- Risk factors associated with mortality (Cox proportional-hazards regression) were
 - low age at the time of HIV diagnosis $p=0.01$ (exp : 0.83, 95% for exp: 0.71- 0.97)
 - absence of ART/HAART $p=0.007$ (exp:4.26, 95% CI for exp: 1.49 - 12.15)

Neurocognitive evaluation (WISC – 1996-1999)



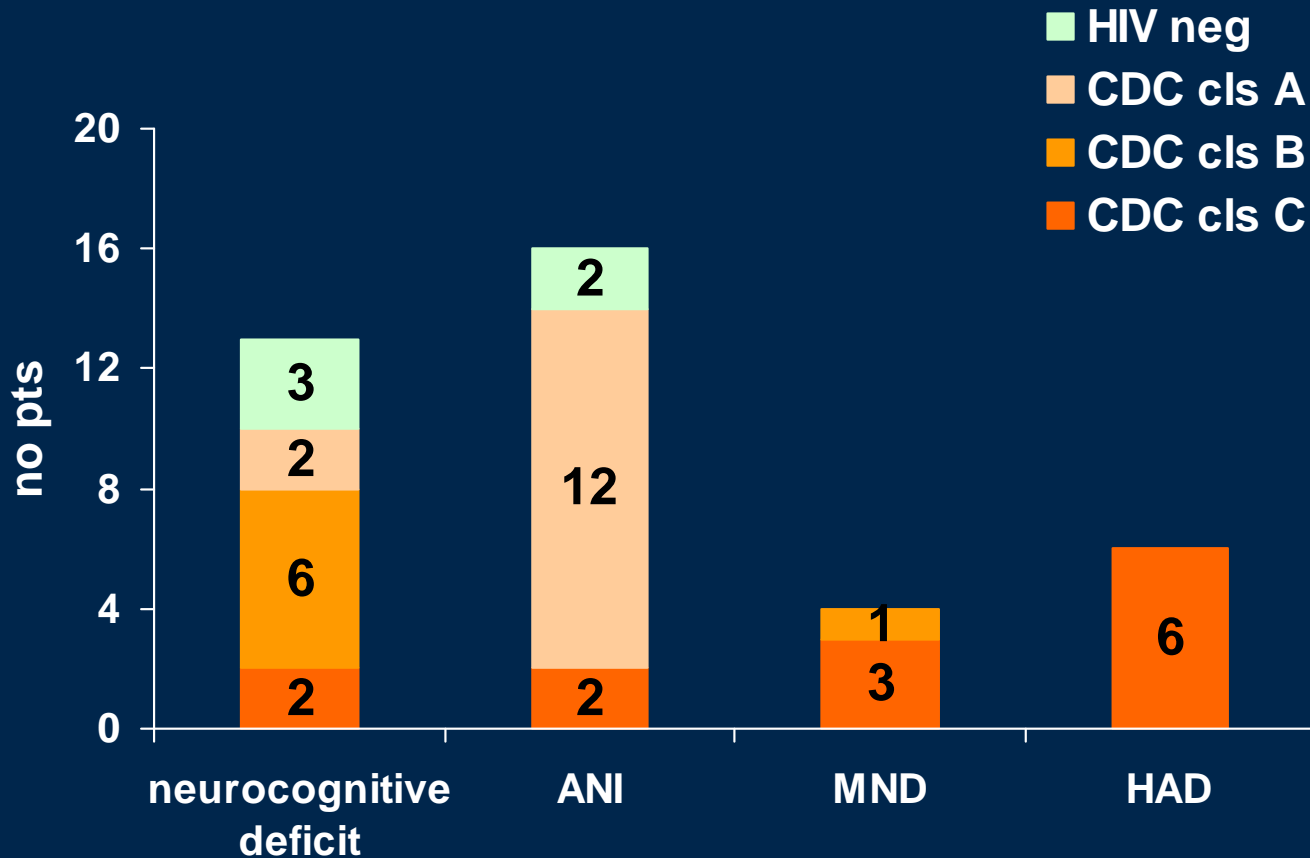
	HIVE group	Children from institutions	Control group
Number	15	12	65
Median age years(limits)	9.5 (7.9-10.3)	8.8 (5.8-10.6)	9.4 (5.4-12.6)
Mean global IQ	62.1	52.2	73.9
Mean performance IQ	57.1	51.1	72.4
Mean verbal IQ	69.3	61.3	81.9

Domain specific impairment rates in Romanian HIV+ young adults



Patients with cognitive impairment according to HAND classification

- 43 HIV+ pts evaluated (CDC clas. A:2, B: 26, C: 15)
- 14 HIV- controls



Overall 60.5% of HIV+ pts had various degrees of neurocognitive deficit

Participants characteristics and neuropsychological test results (HNRC battery)

		HIV- (n=14) mean	SD	HIV+ (n=43) mean	SD	t/χ2	p-value
	Age	18,8	1	18,4	0,7	-1,8	
	Education	11,0	2,2	10,1	1,5	1,6	
	% Male	50%		42%			
	Parent 1 Hollingshead total	46.4	16,3	52.1	12		
	Parent 2 Hollingshead total	47.6	11,3	49.9	14		
	Raw scores						
Verbal fluency	Letter Fluency	35,2	9,7	28,3	10,6	-2,1	0,03
	Animal Fluency	18,8	4,0	17,5	5,0	-0,9	
	Action Fluency	14,2	4,9	11,0	5,3	-2,0	0,05
Speed of Information Processing	Digit Symbol	69,2	15,4	61,4	17,0	-1,5	
	Symbol Search	32,5	7,9	25,9	9,6	-2,2	0,02
	Trails A	39,0	15,8	47,7	20,6	1,4	
	Color Trails 1	44,1	19,4	52,2	23,8	1,2	
	Stroop Word (# of items)	97,0	14,0	88,7	15,0	-1,8	0,07
	Stroop Color (# of items)	71,2	11,5	65,4	12,3	-1,5	
	Stroop Incongruent (#of items)	43,5	15,4	38,1	10,2	-1,5	
Attention and working memory	PASAT-50	33,7	11,4	27,4	11,4	-1,8	0,07
	Spatial Span	16,8	2,9	15,8	4,5	-0,8	
Abstraction/Executive Functioning	Category Test	44,0	21,1	55,1	27,3	1,4	
	WCST-64	9,2	5,9	12,7	6,0	1,8	0,07
	Color Trails 2	78,4	27,2	95,0	49,2	1,2	
Learning	BVMT-R Total Learning	25,7	5,9	23,4	6,4	-1,2	
	HVLT-R Total Learning	27,3	3,8	26,3	4,5	-0,8	
Delayed recall	BVMT-R Delay	9,4	1,9	8,9	2,2	-0,6	
	HVLT-R Delay	9,3	1,9	8,9	2,1	-0,6	
Motor	Pegs Dominant	61,5	6,4	77,6	14,9	3,8	<0,001
	Pegs Non-Dominant	68,5	7,0	83,1	19,1	4,2	<0,001

Discussions and summary (1)

- Our group of parenterally HIV infected children had a different pattern of HIV compared to children with vertically acquired HIV-infection:
 - Fairly low prevalence of HIV in the first years of life
 - Most of them developed HIV after approx. 10 years of chronic HIV-infection similar to the adult population
 - Despite reduction of the number of HIV cases, the prevalence of HIV among AIDS defining diseases did not decrease in the HAART era due to newly diagnosed patients and patients with failure to HAART

Discussions and summary (2)

- Clinical presentation of HIVE included cognitive and/or behavioral changes in most of the children, while neurological exam showed hiperreflexia, cerebelar syndrome and few patients with motor deficit
- CSF exam showed:
 - mildly elevated albumin levels, correlated with pleocytosis
 - higher HIV RNA levels than in plasma for most patients

Discussions and summary (3)

Neuro-cognitive specific evaluation:

- WISC-R testing in children showed
 - marked intellectual deficit in children with HIVE,
 - low performance patterns in the HIVE group but also borderline scores in the HIV + control group
- Most of the adolescents evaluated with the HNRC battery had various degrees of neurocognitive impairment
- Adolescents showed reduced performances mostly in speed of information processing and motor domains

Conclusions

- Prevalence of HIVE among AIDS defining diseases remains significant in the HAART era
- High CSF VL values correlate with the diagnosis of HIVE
- We propose that the current HAND diagnostic criteria are useful tools in detecting the early stages of neurocognitive impairment and neurologic deficits in young patients with HIV clade F

Acknowledgements

Acknowledgements

This work was supported by R21 MH0077487-01 and intramural funding from the HNRC International Core at UCSD.

We also want to thank:

- Drs. Allen McCutchan, Igor Grant and Robert Heaton for helpful discussions
- HNRC team:
 - Terry Alexander and Donald Franklin for personnel training
 - Drs. Sarah Archibald, Christine Fennema and Terry Jernigan for the neuroimaging analyses
- Romanian team: Psych. Andreea Blaglosov and Anca Luca, Nurse Cristina Nitu, Drs. Roxana Radoi, Raluca Erhan, Simona Tetrarov