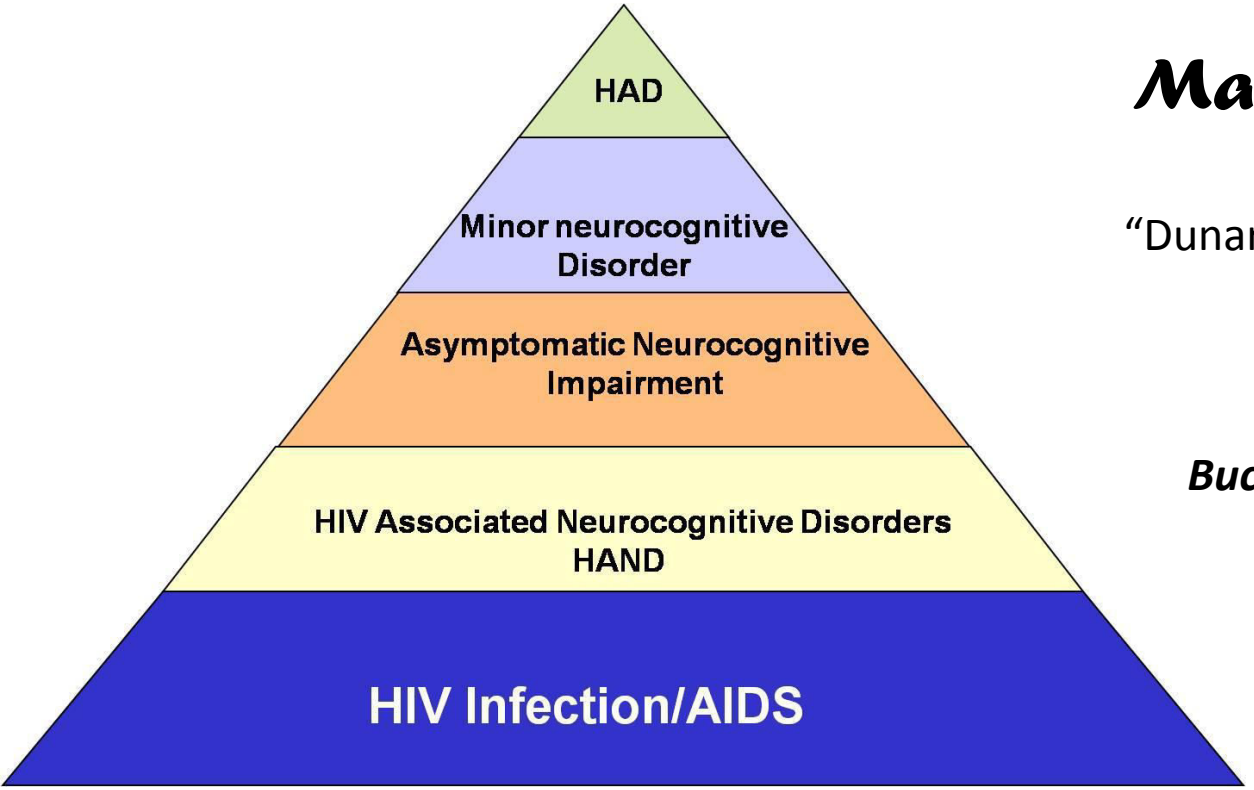
ARROW 2015
Assessment of Resources and Research Opportunities in NeuroAIDS

Neuropsychological assessment in HIV/AIDS and its challenges in Galati County



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Background

- HAND persists despite ARV (~50%).
- Neuropathology in HAART era:
  - less neuronal loss;
  - gliosis, microglial activation;
  - *abnormal protein deposition in brain* increased (immune activation, aging);
  - *synapto-dendritic damage persists.*
- The phenotype of HAND changed:
  - less opportunistic diseases;
  - less severe dementia with marked motor signs;
  - more milder cognitive disturbances;
  - increasing co-morbid conditions: age related metabolic changes, hypertension, mitochondrial aging, substance abuse, viral co-infections [HCV], toxicity of ARVs.

Objectives

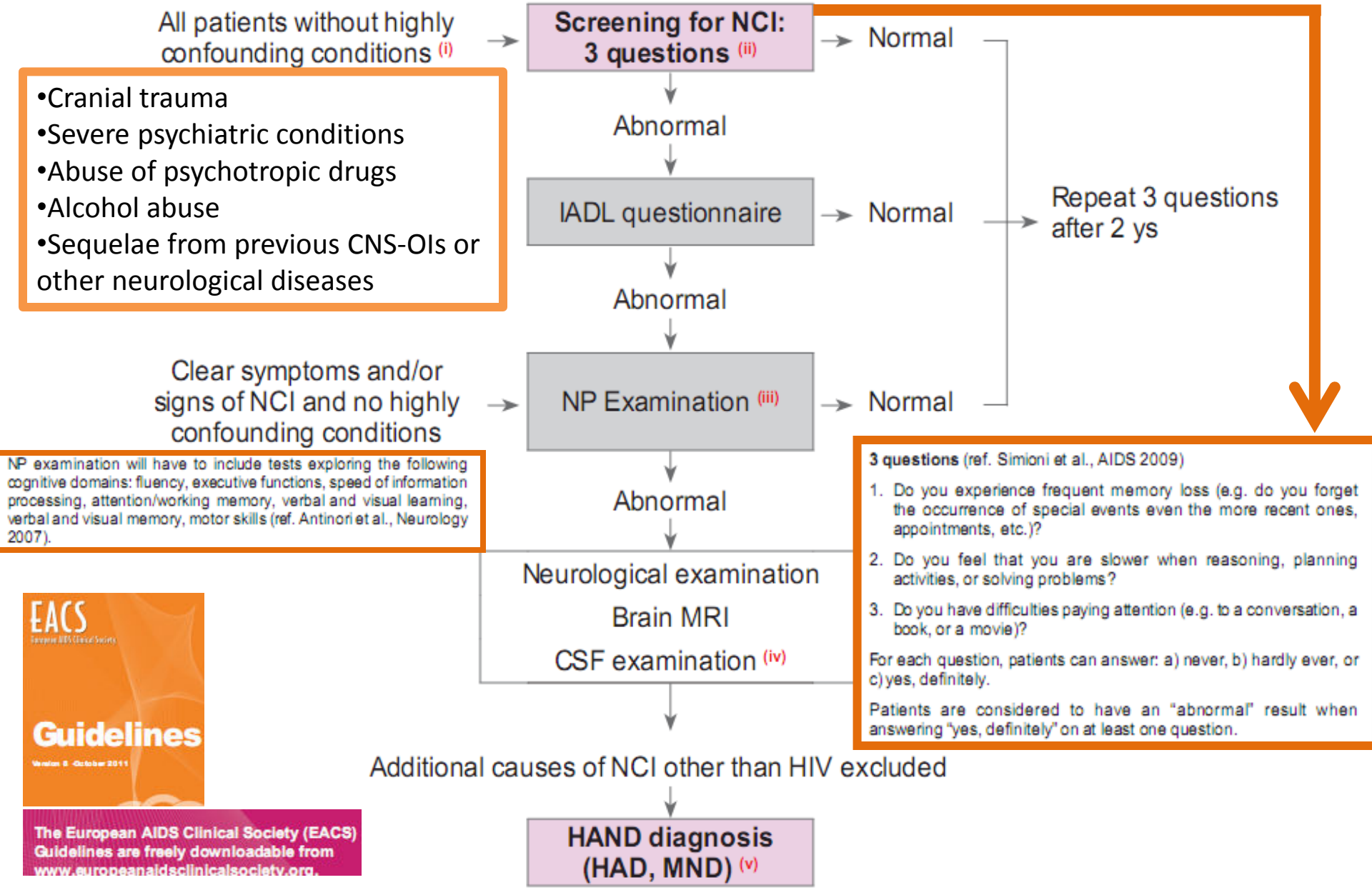
- To calculate the NCD rate on HIV patients from Galati County by screening tests
- To compare the dynamic of NCD by screening tests on pediatric and adult epidemic groups
- To correlate the results of screening tests

Material and Methods

- Prospective study
- HIV/AIDS patients recorded in Galati Clinic
- Screening tests applied in 2 steps: 2010/11 ; 2013/14
  - 3Q test (Simioni)
  - iHDS: 4 items (Max 12 p)
  - Depression Beck inventory (borderline 13)
- Interview based on open question &medical history to identify
- neurocognitive confounding factors
  - Severe psychiatric conditions
  - Sequelae from previous CNS-OIs or other neurological diseases
  - Cranial trauma
  - Abuse of psychotropic drugs
  - Alcohol abuse
- Co-morbid conditions: HTA, diabetes, dyslipidemia, anemia, hipo-vitamin D
- ART CNS-effectiveness scores (Letendre S, 2010).

Neurocognitive Impairment: Diagnosis and Management

Algorithm for diagnosis and management of HIV-associated Neurocognitive Impairment (NCI)



- Cranial trauma
- Severe psychiatric conditions
- Abuse of psychotropic drugs
- Alcohol abuse
- Sequelae from previous CNS-OIs or other neurological diseases

NP examination will have to include tests exploring the following cognitive domains: fluency, executive functions, speed of information processing, attention/working memory, verbal and visual learning, verbal and visual memory, motor skills (ref. Antinori et al., Neurology 2007).

3 questions (ref. Simioni et al., AIDS 2009)

1. Do you experience frequent memory loss (e.g. do you forget the occurrence of special events even the more recent ones, appointments, etc.)?
2. Do you feel that you are slower when reasoning, planning activities, or solving problems?
3. Do you have difficulties paying attention (e.g. to a conversation, a book, or a movie)?

For each question, patients can answer: a) never, b) hardly ever, or c) yes, definitely.

Patients are considered to have an "abnormal" result when answering "yes, definitely" on at least one question.

The European AIDS Clinical Society (EACS) Guidelines are freely downloadable from www.europeanaidsclinicalsociety.org.

International HIV Dementia Scale

Memory-Registration – Give four words to recall (dog, hat, bean, red) (in Luganda: kopo, engatto, doodo, myufo)– 1 second to say each. Then ask the patient all four words after you have said them. Repeat words if the patient does not recall them all immediately. Tell the patient you will ask for recall of the words again a bit later.

1. **Motor Speed:** Have the patient tap the first two fingers of the non-dominant hand as widely and as quickly as possible.
   - 4 = ≥ 15 in 5 seconds
   - 3 = 11-14 in 5 seconds
   - 2 = 7-10 in 5 seconds
   - 1 = 3-6 in 5 seconds
   - 0 = 0-2 in 5 seconds

2. **Psychomotor Speed:** Have the patient perform the following movements with the non-dominant hand as quickly as possible: 1) Clench hand in fist on flat surface. 2) Put hand flat on surface with palm down. 3) Put hand perpendicular to flat surface on the side of the 5th digit. Demonstrate and have patient perform twice for practice.
   - 4 = 4 sequences in 10 seconds
   - 3 = 3 sequences in 10 seconds
   - 2 = 2 sequences in 10 seconds
   - 1 = 1 sequence in 10 seconds
   - 0 = unable to perform

3. **Memory-Recall:** Ask the patient to recall the four words. For words not recalled, prompt with a semantic clue as follows: animal (dog); piece of clothing (hat); vegetable (bean); color (red).
   - Give 1 point for each word spontaneously recalled.
   - Give 0.5 points for each correct answer after prompting
   - Maximum – 4 points.

Total International HIV Dementia Scale Score

This is the sum of the scores on items 1-3. The maximum possible score is 12 points. A patient with a score of ≤10 should be evaluated further for possible dementia.

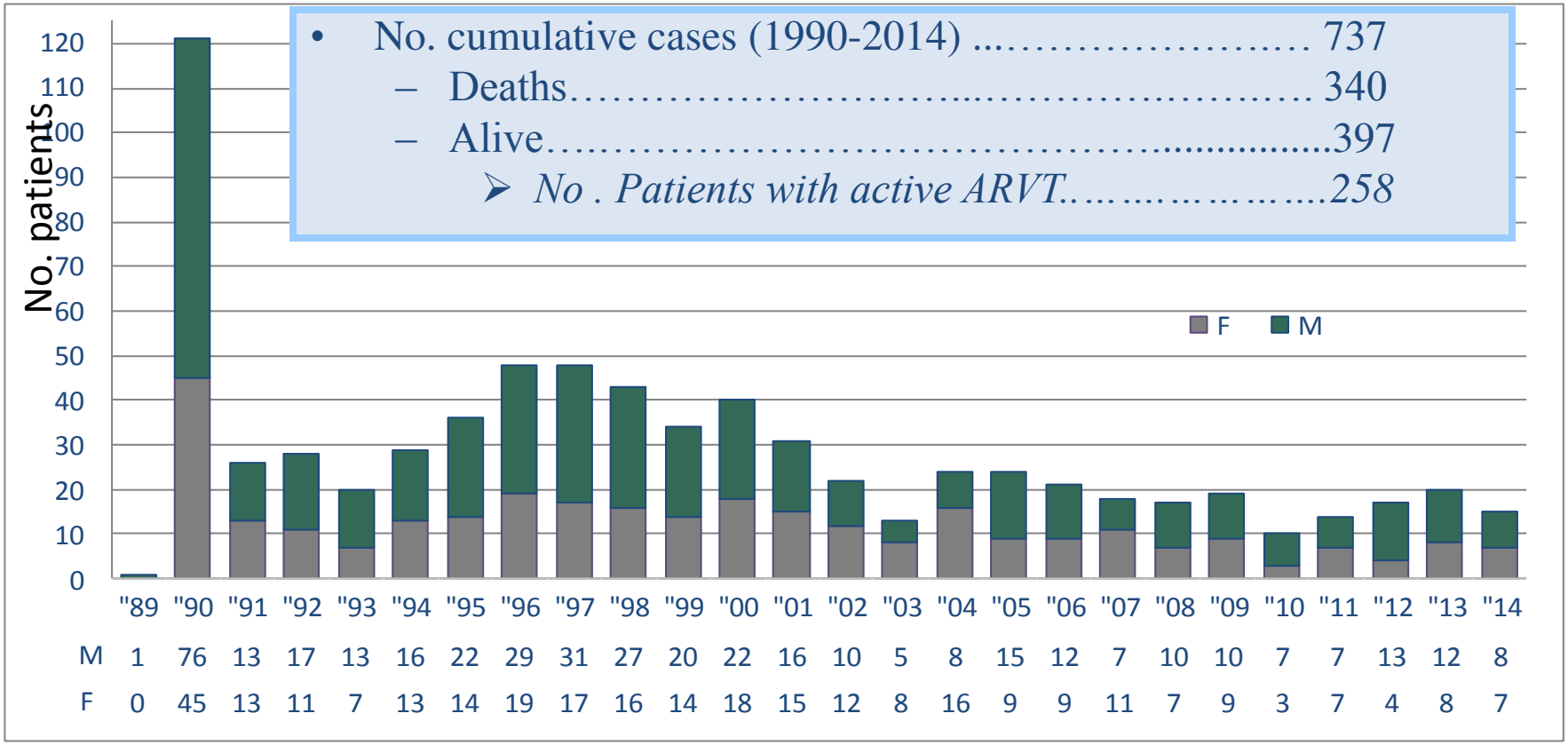
(Sacktor et al. AIDS 2005; 19:1367-1374)

HIV/AIDS EPIDEMIC - GALATI COUNTY
Yearly distribution of the new diagnosed cases: 01.12.2014

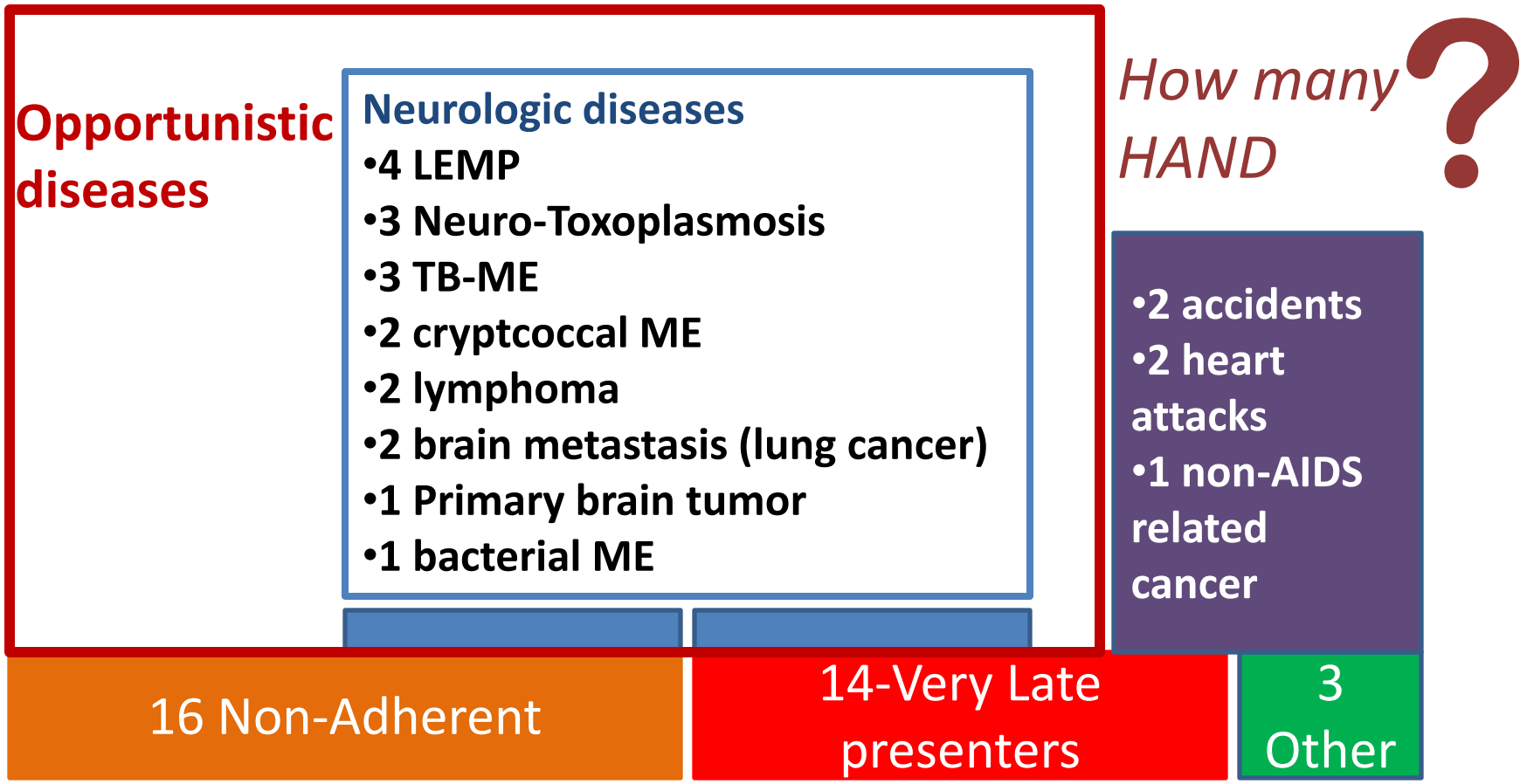
Peculiarity: 2 Epidemic patterns

-pediatric group: cohort (1988-1990)

- Adult group: cases infected in adult age



Causes of Deaths in Galati County (2010-2015)



- Opportunistic infection of the central nervous system raised the risk of death more than 5 times.
- HAND tripled the death risk.
- Diagnosis of any neurologic disorder doubled the risk of death.

P. Vivithanaporn, G. Heo, J. Gamble, H.B. Krentz, A. Hoke, M.J. Gill, C. Power. Neurologic disease burden in treated HIV/AIDS predicts survival: A population-based study. *Neurology.* 2010; 75: 1150-1158.

Variation of “Neuro-AIDS” group of patients

2010
203p

2014
158p

77.3% Follow up the medical care in our clinic

Lost evidence	**9**
Deaths	**8**
Prison	**3**
Spain	3
Italy	10
UK	9
Germany	2
Austria	1
Greece	1

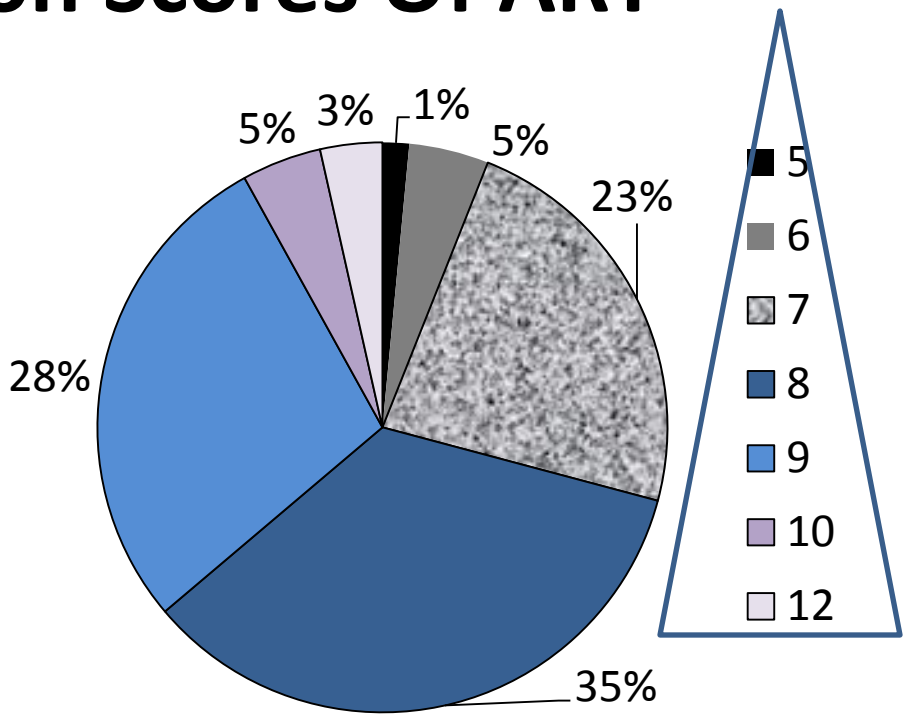
Demographic characteristics

	Pediatric pattern (N=139)	Adult pattern (N=64)	***X2-Test***
Duration of HIV dg.:<5y/5-10y/>10y	0 /22/129	14/36/14	P<0.001
			2T-Test
Median age: 26 [23; 82]	26 [24;30]	37 [23; 82]	P<0.001
Sex: M/F: 99/104	69/70	30/34	OR=1.11 ; p=0.71
Living area U/R: 102/101	68/71	34/30	OR=1.22; p=0.577
Education level < 4 years: 53/150	42/97	11/53	OR=2.04; p=0.050
Institutionalized	21/118	1/63	OR=11.21; p=0.003
Marital status: Single/ Couple	75/64	19/44	OR=2.69; p=0.001
Partner status: +/-	33/16	13/19	OR=3.014; p=0.017
Unknown status of partner	15/64	12/44	P=0.651
Children care 78/125	33/106	45/64	OR=7.6; p<0.001;
Smoking 106/97	71/68	35/29	OR=1.15; p=0.632
Alcohol 37/166	26/113	11/53	OR=1.10; p=1.794

Characteristics of HIV patients

	Pediatric pattern (N=139)	Adult pattern (N=64)	
			2T-Test
AIDS 169/34	126/13	43/21	OR=4.73; p<0.001
Undetectable ARN-HIV: 136/ 67	93/ 46	43/ 21	OR=0.98; p=0.096
HTA 20/183	9/130	11/53	OR=2.99; p=0.017
HCV 3/200	0/139	3/61	OR=0; p=0.010
HBV 56/147	51/88	5/59	OR=6.83; p<0.001
			Mann-Whitney Test
Nadir CD4 Med=157/mm3	140/mm3	242/mm3	P=0.002
Current CD4 583 /mm3	583 /mm3	575 /mm3	P=0.541
Δ Current – Nadir CD4 : 338/mm3	372 /mm3	273 /mm3	P=0.197
Tot. S-Ca Median =9.6mg/dl	9.69	9.45	p=0.027
S-Mg Median=1,98mg/dl	1.96	2.04	p=0.005
Vit D Median=22 mg/dl	21.3	17.9	P=0.028
Triglycerides Median=123 mg/dl	111.8	155.6	P=0.729
Glycemia Median=94.3 mg/dl	94.3	94.3	P=0.592
Hb Median=14.2g/dl	14.12	14.45	P=0.683

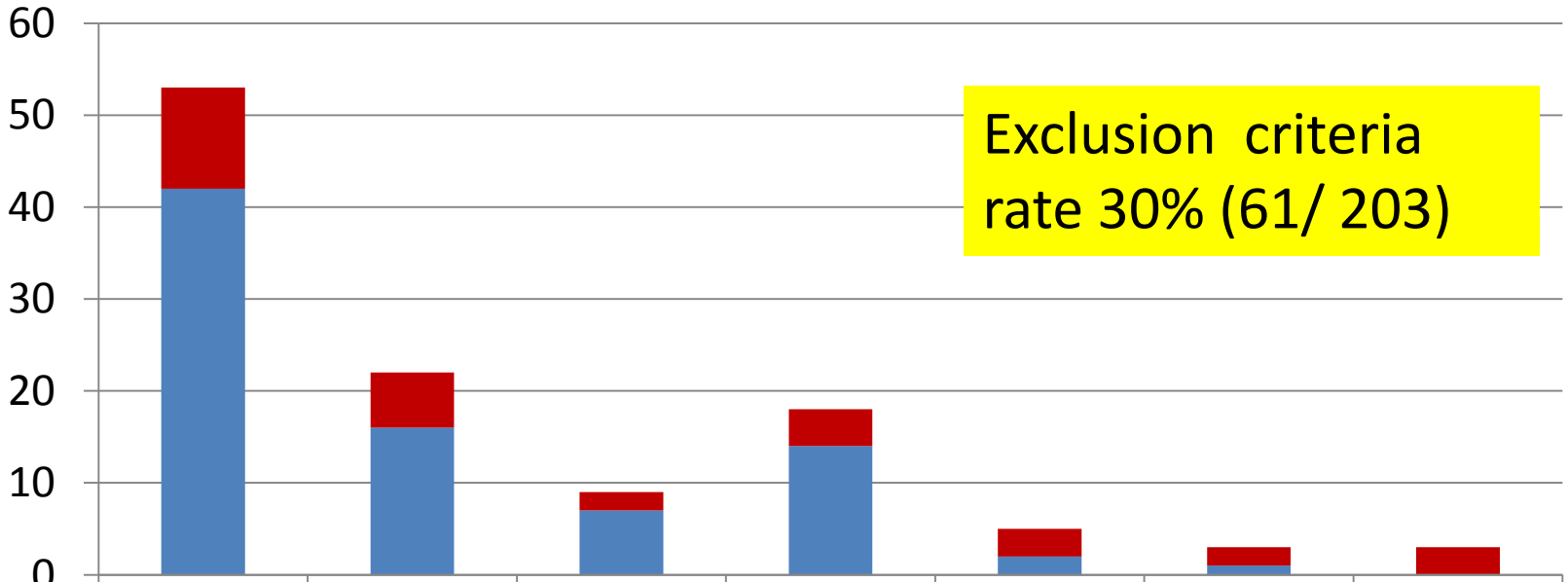
CNS Penetration Scores Of ART



Letendre CNS score

2010/11	2013/14
N1=203	N2=158
Av=7.86	Av=8.14
Med=8 [5;12]	Med=8 [5;12]
61% >7	70.8% >7

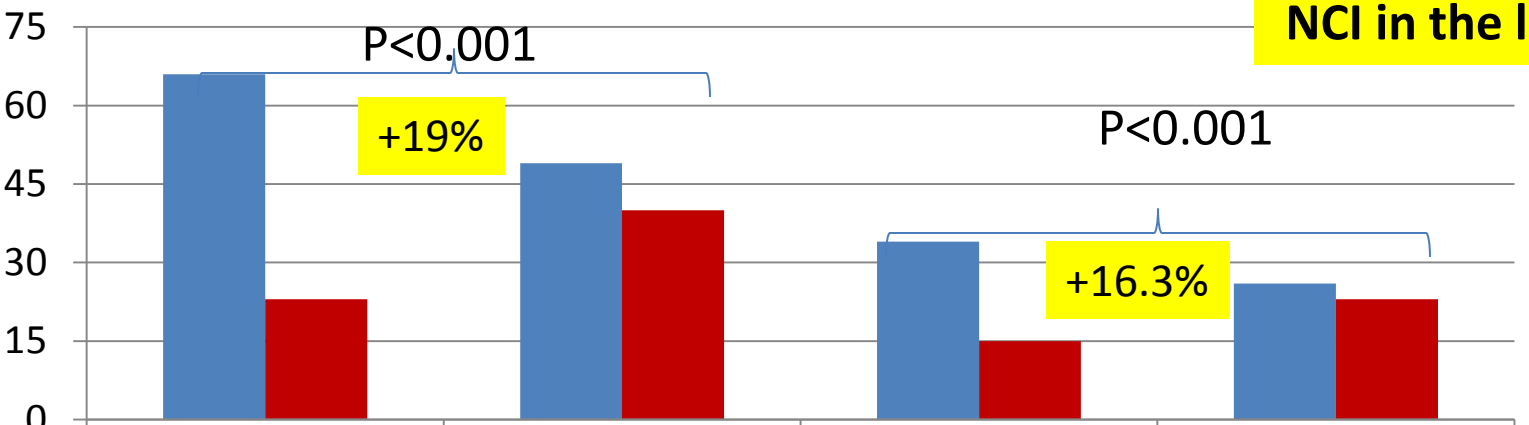
Confounding factors/ exclusion criteria



	Low education	OI	Cranial Trauma	Alcohol	Severe psihiatric	Drugs	Hep-C
Adult	11	6	2	4	3	2	3
Pediatric	42	16	7	14	2	1	0

The dynamic of NCD screening test (3Q)

44.6% NCI (2014); 16.8% progressive NCI in the last 2 y



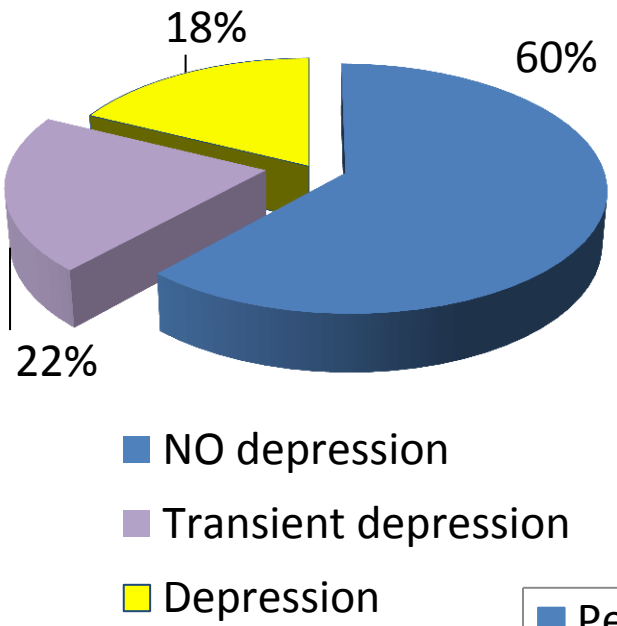
	Pediatric-I	Pediatric -II	Adult -I	Adult -II
3Q-0	66	49	34	26
3Q-1	23	40	15	23

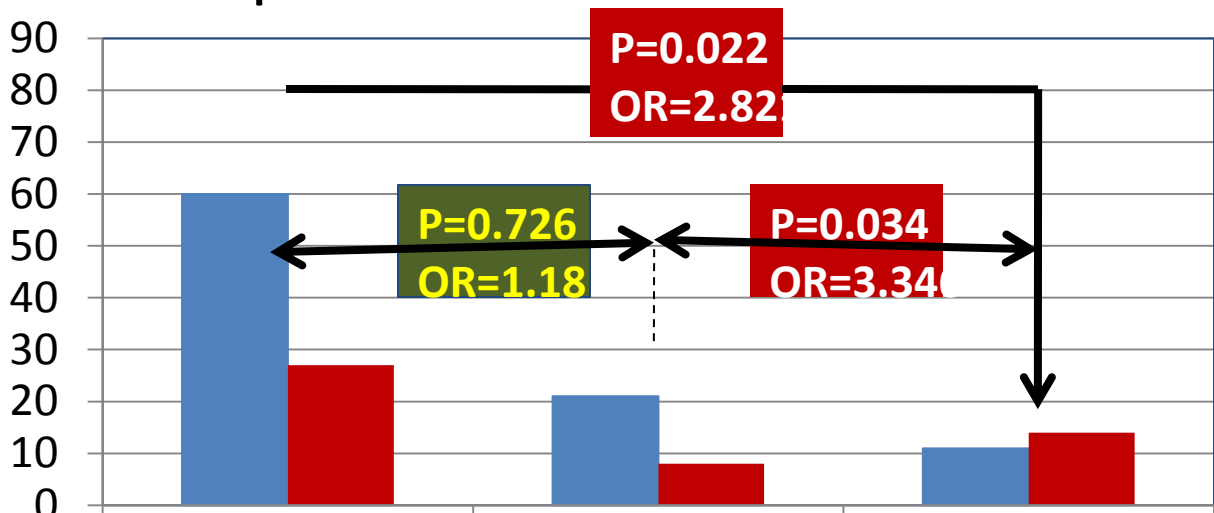
NCI screening: 3 questions

1. Do you experience frequent memory loss (e.g. do you forget the occurrence of special events even the more recent ones, appointments, etc.)?
2. Do you feel that you are slower when reasoning, planning activities, or solving problems?
3. Do you have difficulties paying attention (e.g. to a conversation, book or movie)?

For each question, answers could be: a) never, b) hardly ever, or c) yes, definitely. HIV-positive persons are considered to have an "abnormal" result when answering "yes, definitely" on at least one question

Depression in HIV patients from Galati





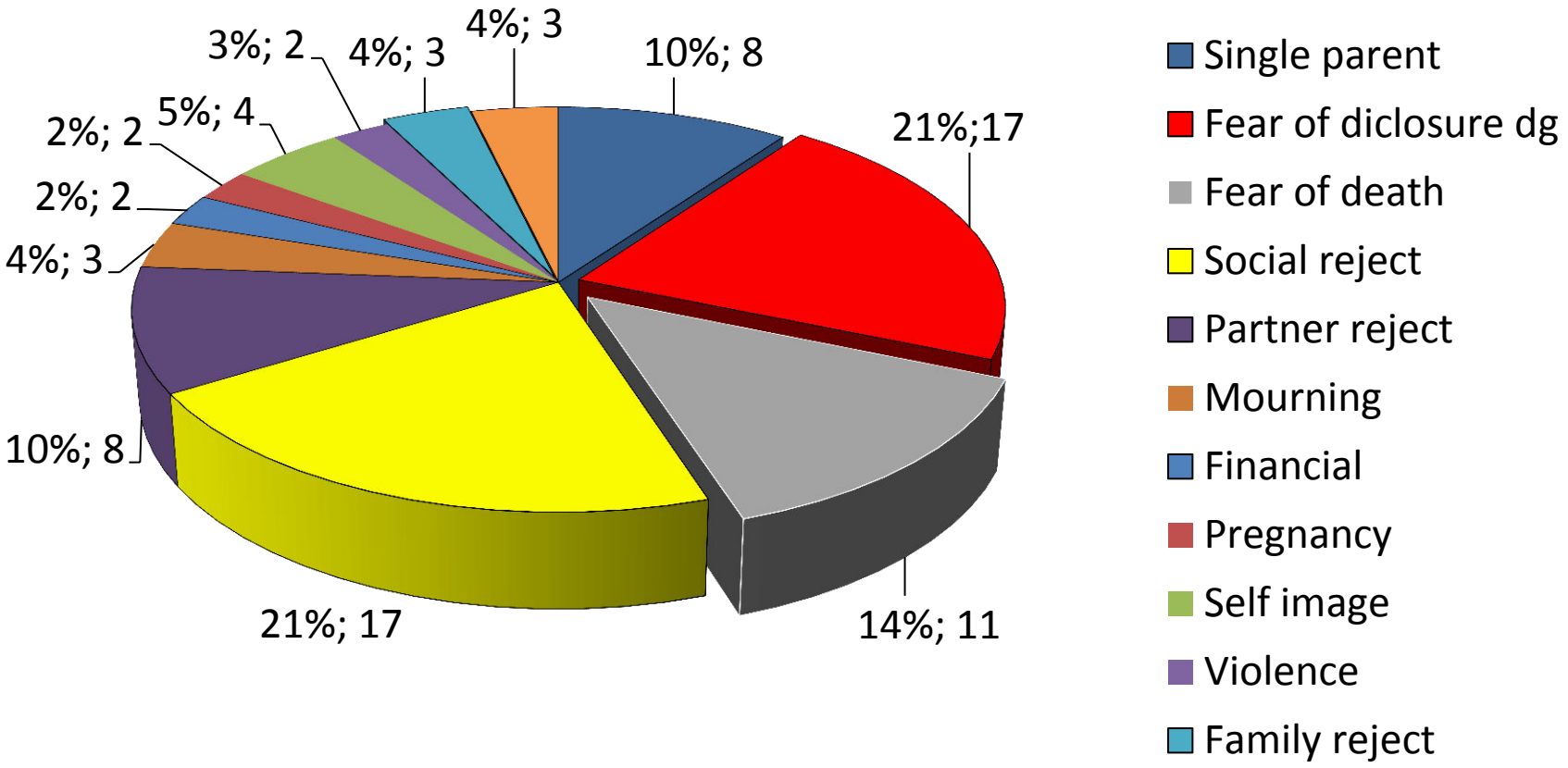
	No depression	Transient depression	Depression
Pediatric	60	21	11
Adult	27	8	14

Transient depression: Beck score>13 in one evaluation
Depression: Beck score> 13 in both evaluations
No depression: Beck score< 13 in both evaluations

Challenges:

- Depressive mood is changing along the time
- Overlap in signs and symptoms of HIV disease and depression
- Symptoms such as anorexia, weight loss, fatigue, insomnia difficult to attribute to either depression or HIV/OI

Reasons for depression or transient depression



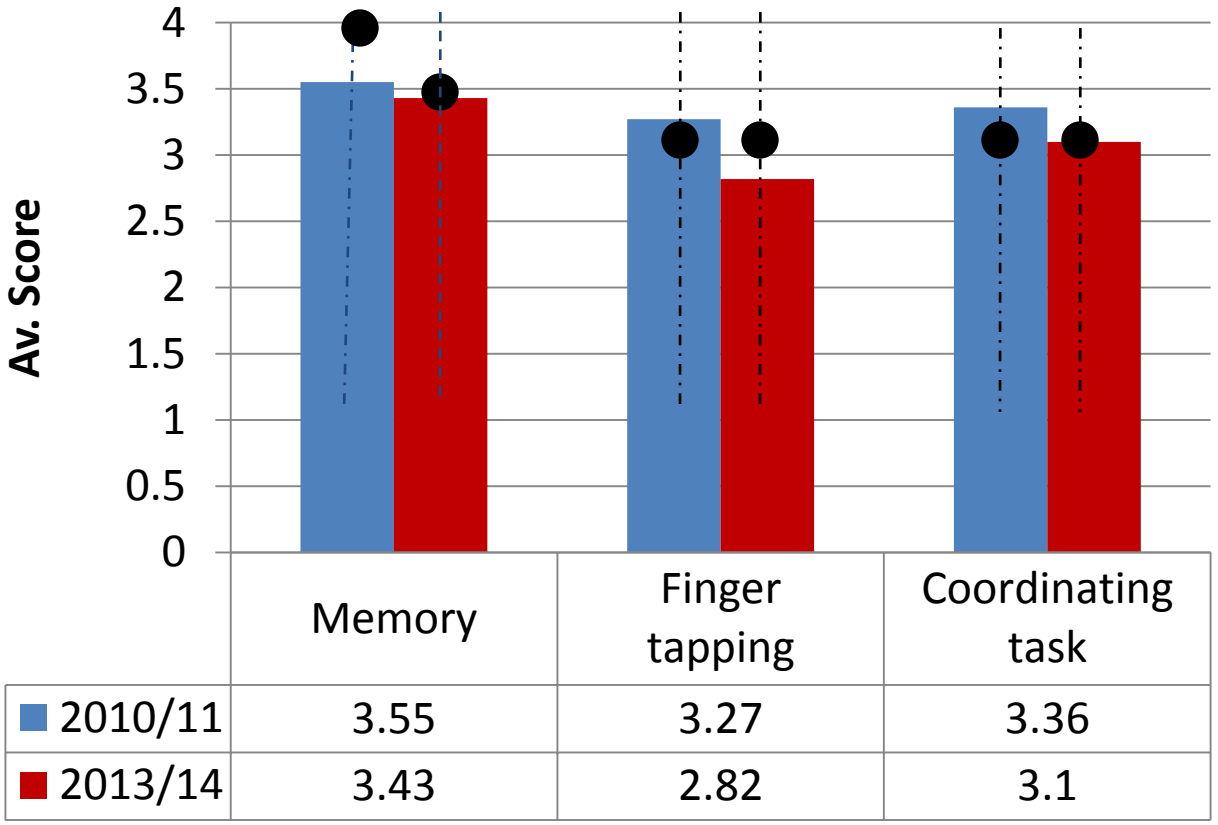
- Depression - Social reject: p=0.005
- Transient depression - Partner reject: p=0.028

- Median IQ (pediatric)

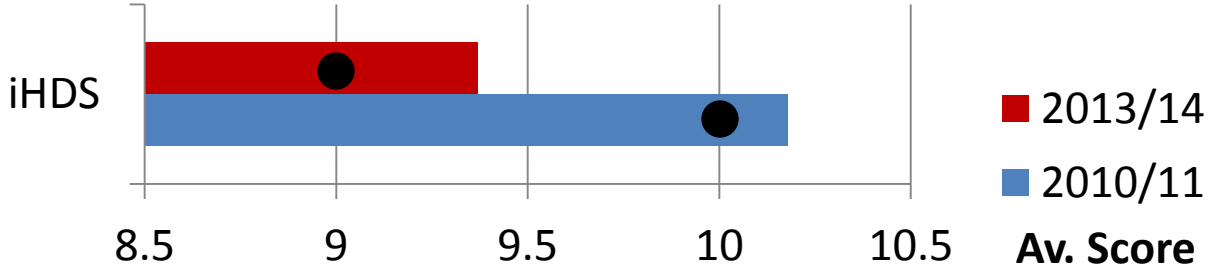
No > Transient > Depression

90.5 > 81.5 > 71.5

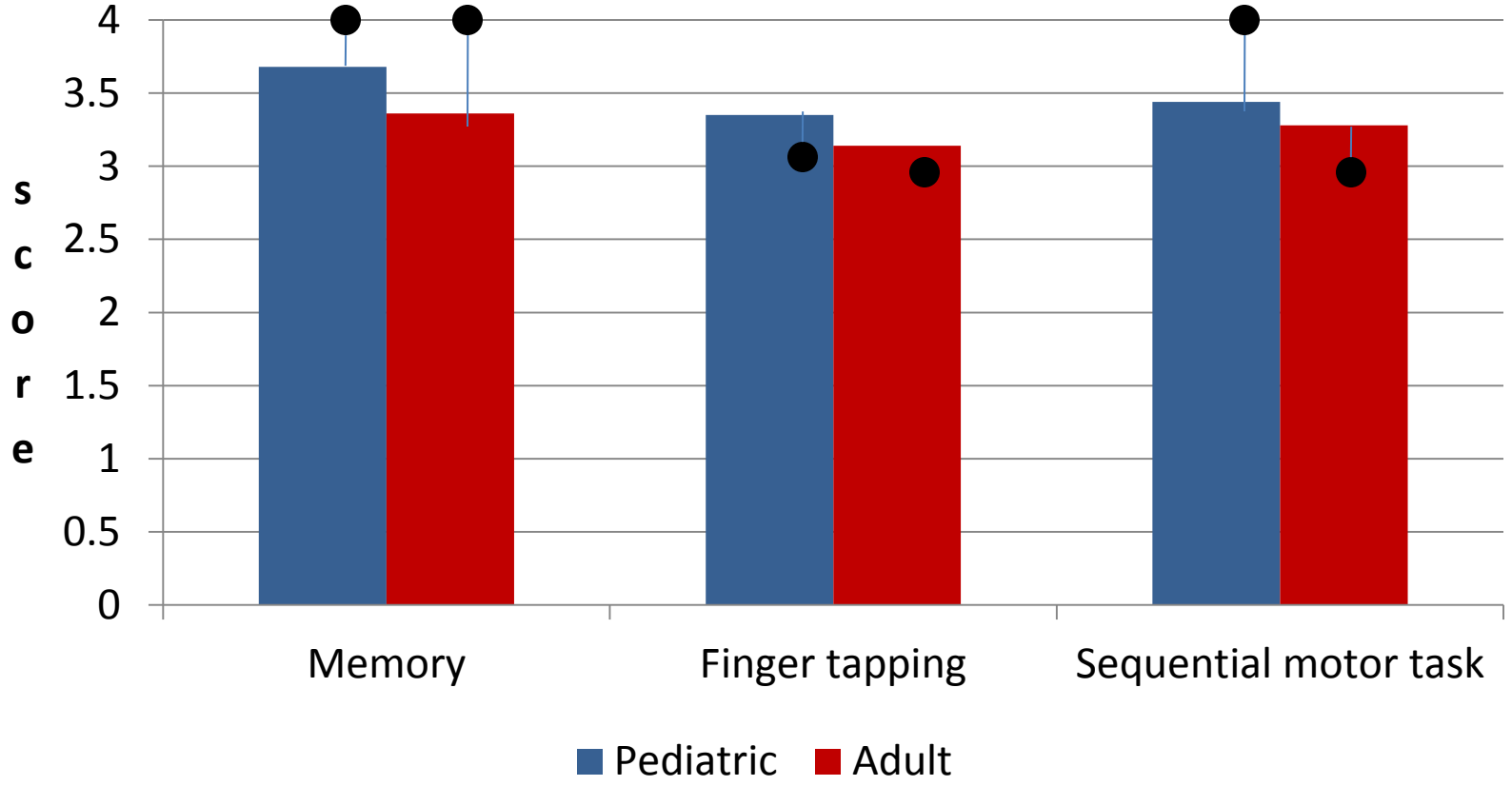
The Dynamic of iHDS Screening Test

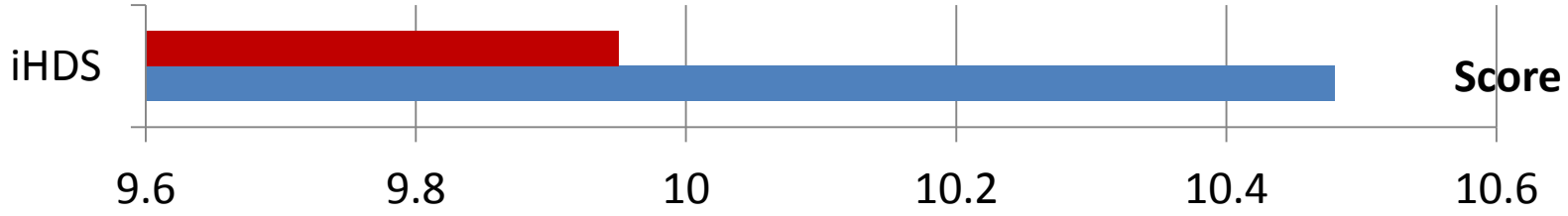


	Memory	Finger tapping	Coordinating task
2010/11	3.55	3.27	3.36
2013/14	3.43	2.82	3.1

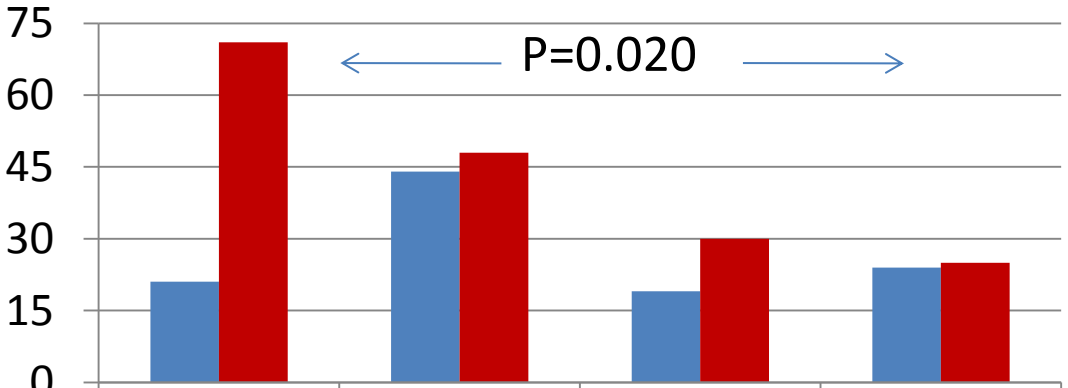


Comparative Median and Average Scores of HDS Items





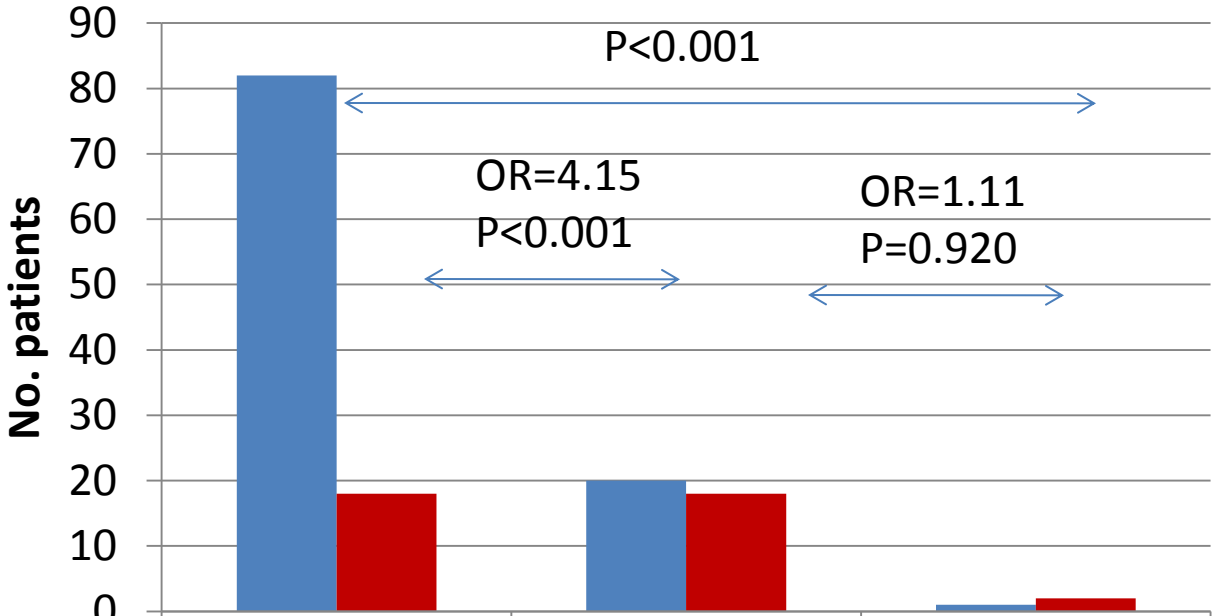
Comparative Dynamic of HDS In Pediatric and Adult HIV Groups



	Pediatric-I	Pediatric - II	Adult -I	Adult -II
iHDS<10	21	44	19	24
iHDS>=10	71	48	30	25

22.8%	47.8%	38.7%	48.9%

Correlation of 3Q Test and iHDS Test



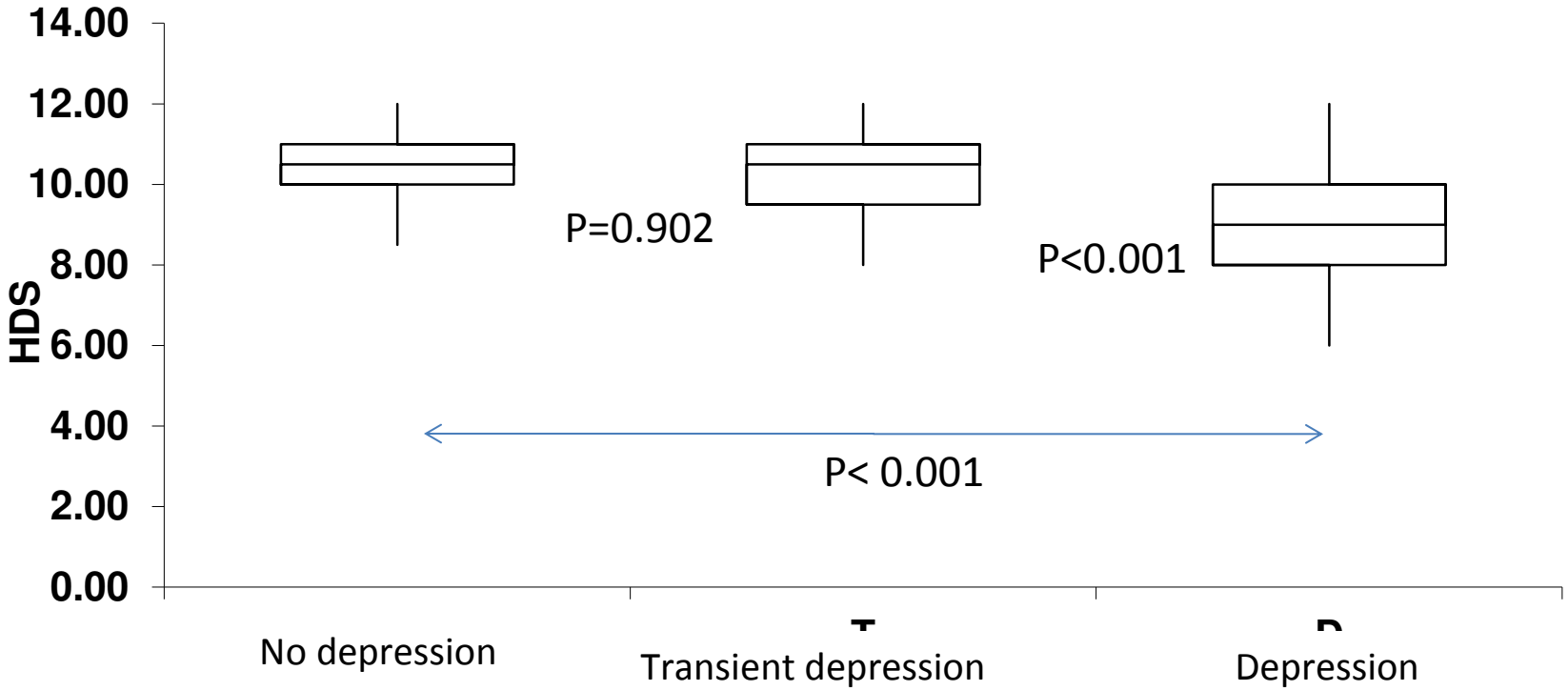
	iHDS>=10	iHDS (10; 8]	iHDS<8
3Q-0	82	20	1
3Q-1	18	18	2

iHDS-1: >10 (normal)

iHDS-2: 8-10 (mild disfunction)

iHDS3: <8 (severe disfunction)

Correlation of iHDS and depression



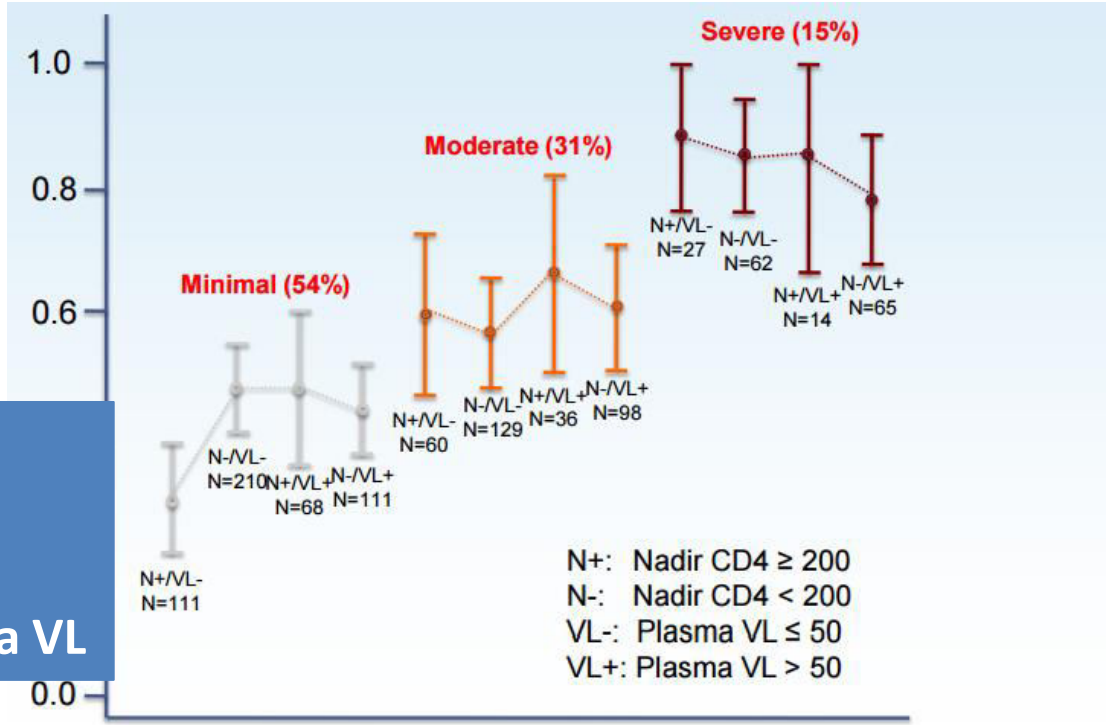
Median HDS	**11**	**10.5**	**9**

Correlations of NCD Tests and HIV Markers

	ARN-HIV (det/undet)*	nadir CD4
3Q-test	p=0.151	p=0.300
iHDS	p=0.677	p=0.020
Depression	➢Transient : OR=3.13; p=0.012 ➢No : OR=2.08; p=0.143	p=0.627

➢ARN-HIV – CNS penetration score: p<0.001

**baseline ARN-HIV was not systematically available*

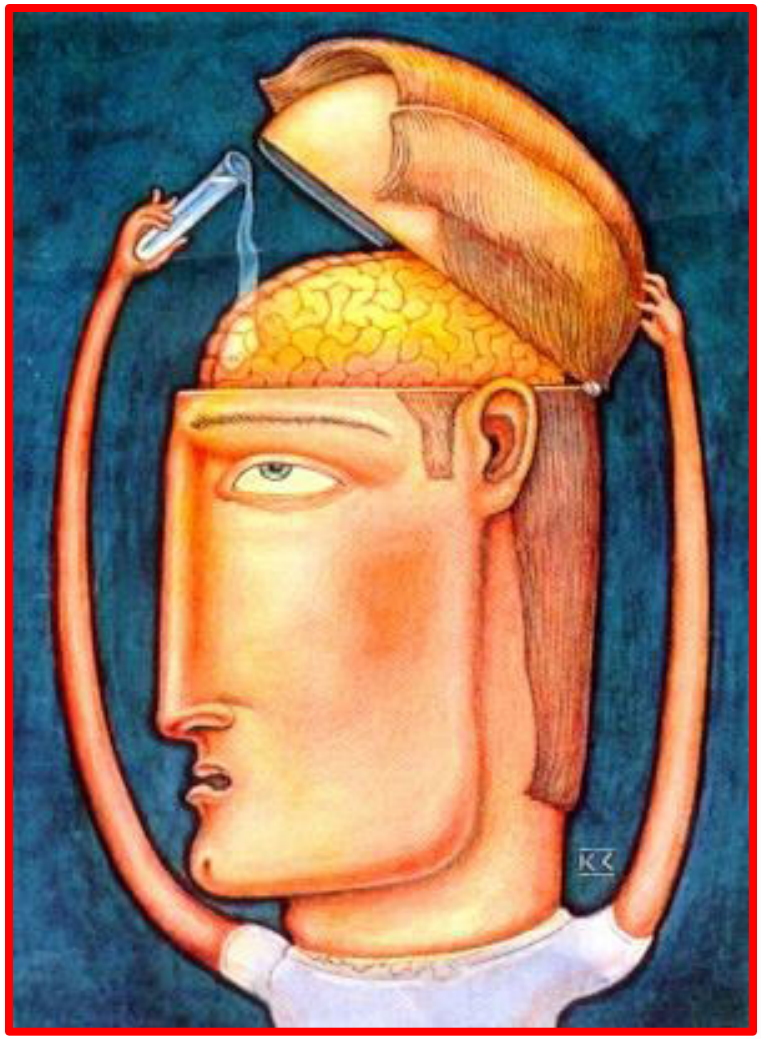


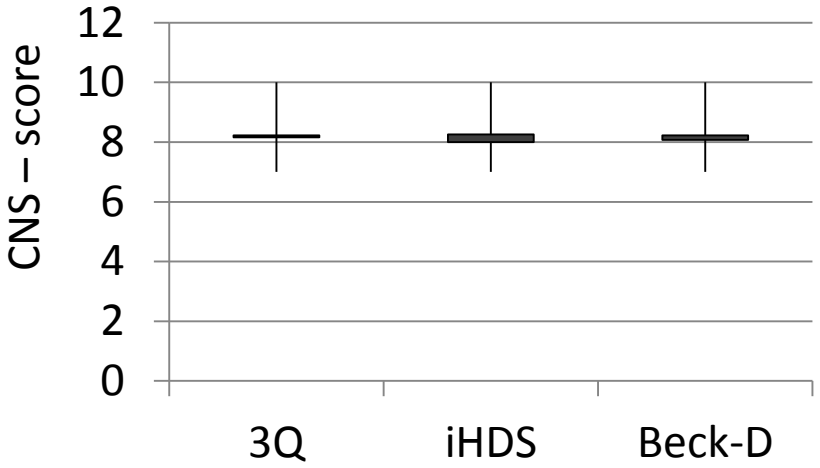
HAND in HAART Era
Occurs at higher CD4 counts
Course stable or oscillating
Occurs with undetectable plasma VL

Letendre et al, 16th CROI 2009, Abstract 484b

Heaton et al, Neurology 2010;75:2087–2096

Does CNS penetration profile matter ?



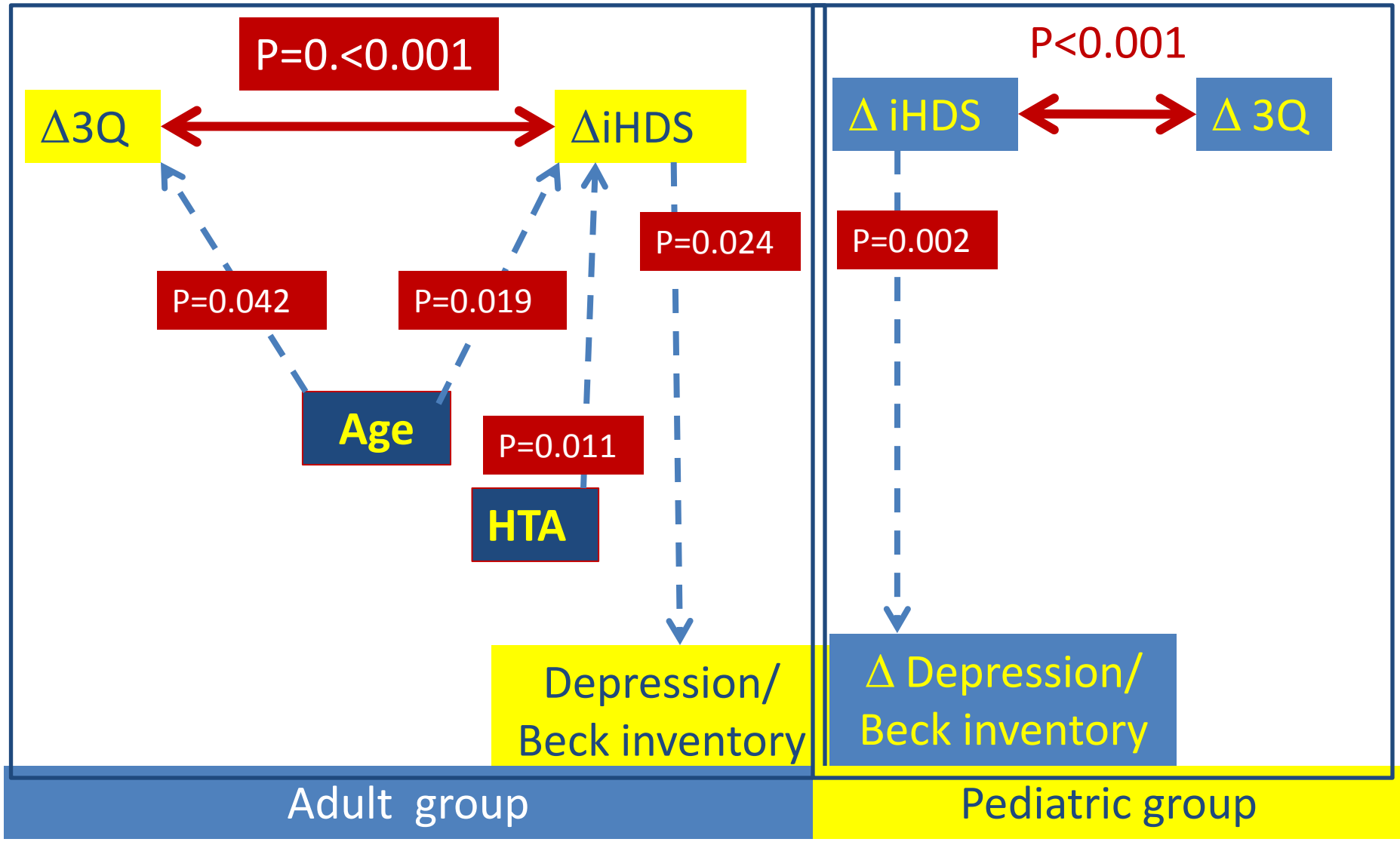


NO effect on 3Q, iHDS or depression

- *Sacktor N, 2001:* no effect on cognitive function
- *Cysique L, 2004:* effect only in cognitively impaired
- Marra C., 2009 ~ CNS penetration associated with lower CSF HIV RNA but *worse* cognitive performance
- *Letendre S., 2007* ~ new index of penetration

From JC McArthur, MBBS, MPH, at 13th Annual Ryan White HIV/AIDS Program Clinical Conference, IAS–USA.

Correlations of NCI variation by screening tests



Discussions

Limits:

- Shotcoming of more comprehensive reference NP tests
- Low performance of screening instrument as iHDS (Brunett J, 2013).
- Deepening investigations as HIV-VL in CSF, MRI or complex NC tests were achieved by few of our patients.
- The reasons for incomplete protocol:
  - High costs of MRI;
  - Difficulties to obtain the consent for lumbar puncture;
  - Refuse to go in other setting to be hospitalized.

Challenges for improving early detection of HAND:

- To use biomarkers for detection of predisposition, diagnostic and monitoring;
- To develop more accurate NP tests.

Conclusions

1. The frequency of NCD according 2 screening tests is 44% (3Q) and 48% (iHDS), consistent with other studies (Heaton, 2010).
2. Along the 4 years, screening tests mark the progression of NCD.
3. Most patients with NCD have mild dysfunctions.
4. The adult group is more severe affected due to the old age and more frequent hypertension, while the pediatric group seems to be faster impaired.
5. The results of NC screening tests are not influenced by HIV current markers or CNS penetration score.
6. IHDS score correlates with nadir CD4, as a hallmark of neurological damages established before initiation ARVT.
7. Mild cognitive impairment associated with HIV requires to improve screening tools and treatment interventions in order to improve the care and the quality of life for individuals living with HIV and AIDS.

References

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Thank you!
Galati, Danube River