Week 48 Cognitive Improvement in HAND After Switch to HAART based on CHARTER score +3 - *Neuro+3 Study*

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Background:

·HIV-associated neurocognitive disorders (HAND) are increasingly frequent despite plasma virological suppression on ART (prevalence between 30 and 50%).

· Low CNS Penetration Effectiveness (CPE or CHARTER) score is associated with a greater risk of HIV replication in CSF[1,2,3] and with greater risk of HAND[4].

· Better CPE is known to prevent HAND[5] , but in a little retrospective cohort paradoxical results have suggested the possibility of drug-induced neuronal toxicity[6].

Study Design: Neuro+3 study is a pilot open-label study in virologically controlled patients for more than one year, aiming to demonstrate a significant improvement in HAND when antiretroviral (ARV) regimen is changed to new combination with CPE improved ≥+3 points and total CPE ≥ 9. HIV patients were screened with Test of Frontal Efficiency BREF ≤15/18 and/or modified-HIV Dementia Scale ≤10/12 to undergo a standardized battery of 10 tests and 6 domains studied (cf. Table 2). Raw test scores were converted to obtain a Global Deficit Score[7] (GDS) for each patient, and a GDS_d (GDS *by domain*) where only the worst result for each domain was considered. Each patient was classified into HAND levels[8] (i.e. *Asymptomatic Neurocognitive Impairment* (ANI); *Mild Neurocognitive Disorder* (MND); *HIV-Associated Dementia* (HAD)) using the Cognitive Complaint Questionnaire (CCQ), the Inventory of Activity Daily Living (IADL part II), and assessment scores. Brain MRI and CSF exam were performed to detect other cerebral disease. Ultrasensitive HIV-RNA in plasma and CSF were measured. Concentrations of ARV drugs were obtained at baseline and follow-up. After inclusion, current ARV was changed to a new combination with enhanced CPE (≥+3) and the same battery of cognitive tests was performed after 48 and 96 weeks. Data of W48 are analyzed in the present study.

Inclusion Criteria: informed consent; age between 18 and 65; plasma HIV-RNA <500 copies/mL during the past year; at least 2 altered neurocognitive domains by at least one standard deviation.

Exclusion Criteria: acute vascular or infectious disease of the CNS; positivity for HBsAg or HCV serology; drug or alcohol abuse; hypothyroïdism; vitamin B deficiency; psychiatric troubles; inability to undergo brain MRI or CNS analyses; impossibility to improve over existing CPE; only one altered ability domain; severe depression BDI II ≥29 (moderate depression allowed inclusion when corrected BDI II <20 without physical 15-21 questions, because correlation between CSF HIV-RNA and depression[9]).

Table 1: Baseline Characteristics

31 patients	Median results
Age (years)	54 (85%≥45; all<65)
Sex	26 men, 5 women
Educational level (years)	11 [5-17]
Professional activity	20 / 31pts
Risk factors:15smoking,14dyslipidemia, 7HTA, 5 hereditary, 2 diabetes	Framingham score: 5 [0-12]
HIV infection duration (years)	19 [2-29] (74%≥15years)
Current ARV therapy duration	3.25 years
Undetectable plasma HIV-RNA duration	6.58 years
CD4 count (/mm3): Nadir / At screening	165 (58%<200) / 622 (29%<500)
Plasma HIV-RNA at Baseline (copies/mL)	2 (22≤5cp/mL;2>20cp/mL:26, 40)
CSF HIV-RNA at D0 (copies/mL)	<1 (9pts >5cp/mL: 7.10.10.38.41.47.48.64.78)
CPE at baseline (3.1 drugs/pt)	6 [3-8]; NRTI 90%; NNRTI 26%; PI 61%; II 36%; Entry I: 0%
CPE after new combination (3.8 drugs /pt)	10 (all scores ≥9 except 2pts); NRTI 84%; NNRTI 45%; PI 55%; II 97%; Entry I: 36%

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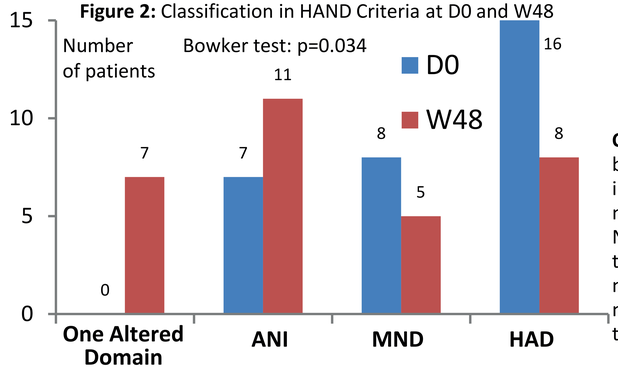
Table 2: Evolution of tests results between D0 and W48; p*=McNemar test; p**=Wilcoxon test

Battery of tests	Altered tests at D0 (%)	Altered tests at W48 (%)	p*	Average deficit score at D0	Average deficit score at W48	p**
Grooved Pegboard (dominant)	51.6	45.2	0.754	1.74±2.14	1.65±2.2	0.551
Grooved Pegboard (non dominant)	58.1	45.2	0.344	1.74±2	1.48±2	0.508
Grefex Verbal Fluency	67.7	61.3	0.754	1.39±1.38	1.16±1.29	0.210
California Verbal Learning Test (CVLT)	67.7	48.4	0.070	1.35±1.28	0.97±1.25	0.115
Digit Span WAIS III	38.7	38.7	1.0	0.77±1.2	0.87±1.38	0.635
Paced Auditory Serial Addition Test (PASAT)	87.1	74.2	0.219	4.03±1.82	3.16±2.25	0.008
WAIS III Digit Symbol Test	41.9	45.2	1.0	1.03±1.45	1.1±1.47	0.775
Trail Making Test Grefex Part A	22.6	19.4	1.0	0.65±1.47	0.65±1.56	1.0
Trail Making Test part B (or B-A)	54.8	41.9	0.219	1.87±2.16	1.42±1.95	0.207
Wisconsin Card Sorting Test (WCST) Grefex	35.5	25.8	0.453	1.42±2.19	1.1±1.96	0.242

Figure 2: Classification in HAND Criteria at D0 and W48



Results and Discussion: 63 HIV patients were screened, 31 enrolled between 2012 and 2014, Baseline Characteristics shown in Table 1. Drugs measurements at D0 showed that 28 drugs were undetectable in CSF (29%) and a poor adherence to some treatment could be suspected. The median duration between D0 and W48 cognitive tests was 436 days (≥1 year for all patients to prevent learning effect). Data showed improvement for tests with significant difference for GDS, GDS_d, the number of altered cognitive domains, CCQ and BDI II scores (Figure 1) and PASAT (Table 2); HAND classification (Figure 2) showed a significant evolution (Bowker test, p=0.034) with improvement in 52% (16 pts), no change in 45% (14pts), and worsening in 3% (1pt). The hypothesis of the study was a better control of persisting HIV replication in CNS, but there was no significant difference on cognitive improvement between the 9 patients with HIV replication in CSF, compared to other patients. No significant correlation was found between cognitive improvement and the intensification of any drug class. Because the majority of included patients were active professionals, IADL was normal for almost all pts, and classification in HAND criteria was essentially based on Cognitive Complaint Questionnaire (CCQ), a subjective value. Nevertheless, the improvement of standardized tests with GDS was correlated with CCQ at W48 (p=0.032, Fisher's test). During the study, 8 pts had transient neurologic adverse events (one pt had pre-existing persistent moderate depression). Patients had significant improvement for Beck depression score and they did not have change in their antidepressant treatment (6 pts), but no correlation was found with GDS improvement.

References:
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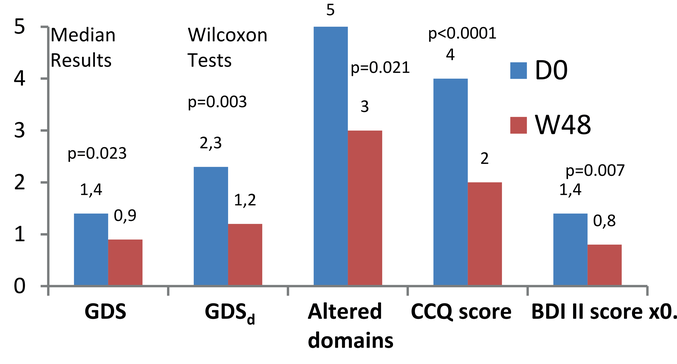
Figure 1: Evolution of Cognitive Results between D0 and W48



Conclusion: Neuro+3 Study enrolled 31 patients with HAND documented by cognitive tests, brain MRI and CSF exams. The population was very homogeneous: long duration of HIV infection, CD4 nadir <200/mm3, undetectable plasma HIV-RNA since many years. The initial median CPE score of 6 was improved to 10 after treatment modification with introduction of NNRTI, II and CCR5 inhibitors. After a duration of one year with the new ART combination therapy, W48 data showed that ARV intensification with better CPE score in patients with neurocognitive impairment was associated with significant improvement in standardized neuropsychological tests and in patient's cognitive complaint, without evidence of neurologic toxicity.