DAA IMPROVE VACS BUT DO NOT INFLUENCE COGNITIVE IMPAIRMENT IN HIV/HCV COINFECTED

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Background
The role of HCV as an independent risk factor for HIV associated neurocognitive impairment (NCI) is still controversial. VACS Index, a composite marker of disease severity, has been associated with increased risk for mortality and with concurrent risk for NCI. Aim was to evaluate changes over time after DAA treatment on neurocognitive performance and VACS index in HIV/HCV coinfected (HIV/HCV) patients (pts).
Methods
HIV/HCV pts starting DAA treatment were enrolled in a prospective study. All patients underwent neuropsychological assessment (NPA) before starting DAA (T1) and 12-24 weeks after (T2) end of treatment (EOT). NPA was carried out through a standardized battery of 14 tests on 5 different domains. We used NPZ8 as a summary measure of zscores of neuropsychological testing performance. Pts were classified as having NCI if they scored >1 standard deviation (SD) below the normal mean in at least 2 tests, or >2 SD in 1 test. HAND was classified according to Frascati's criteria. VACS Index was calculated through standard methods at T1 and 6 months after EOT. Paired Wilcoxon and Mc Nemar test were used for statistical comparisons.
Results
A total of 62 patients included: male 74.2%, median age 54 years (IQR 5156) ; injection drug users (IDUs) 85.4%; on cART 100%; median CD4 563 cell/mmc (IQR 340761); HIVRNA not detectable 83.3%; baseline log10 HCV RNA 5.8 (IQR 5.36.3). Fibrosis was F1/F2 in 11, F3 in 12, F4 in 39 pts. Half of the patients was HCV treatment experienced. DAA regimen was SOFbased for 32 pts and nonSOFbased for 30 pts. At baseline 23/62 were neurocognitively impaired. HAND criteria were limited by high frequency of confounding comorbid conditions (substance use).
No significant changes over time in NPA was observed after DAA (Fig. 2a). Similarly, when considering only pts achieving SVR12, neurocognitive performance did not improve. For 51 pts (Fig. 2b), VACS index was calculated at T1 and 6 month after EOT: at month 6 compared to T1, median values were significantly lower after DAA treatment (Fig. 2).
Conclusion
In our experience, DAA treatment strongly improved VACS Index, but did not impact on neurocognitive performance in HIV/HCV coinfected. These results could be explained by a poor contribution of HCV to neurocognitive impairment in HIV coinfected population, even though the elevated frequency of confounding factors in this highly vulnerable population may have masked benefit effect of DAA on neurocognition.

BACKGROUND and AIM

❖The role of HCV as an independent risk factor for HIV-associated Neurocognitive Impairment (NCI) is still controversial[1,2]

❖Treatment with Direct Acting Antivirals (DAA) regimens is a more successful and tolerable option to eradicate HCV; in this contest, it is of great interest to clarify the contribution of HCV to HIV-associated NCI

❖The Veterans Aging Cohort Study (VACS) Index is a composite marker of disease severity based on routine clinical blood tests[3] and it has been consistently associated with increased risk for mortality[4] and morbidity[5]

❖The VACS Index has also been linked to concurrent risk for NCI [6,7]

***Aim** was to evaluate changes over time after DAA treatment on neurocognitive performance and VACS index in HIV/HCV co-infected patients*

METHODS

Single-center, prospective analysis of HIV/HCV co-infected patients starting DAA treatment with the neuropsychological assessment (NPA) performed and the VACS Index calculated.

✓ **NPA** was carried out through a standardized battery of 14 tests on 5 different domains, before starting DAA and 12-24 weeks after end of treatment (EOT).
We used NPZ8 as a summary measure of z-scores of neuropsychological testing performance.
We classified patients as having NCI if they scored >1 standard deviation below the normal mean in at least 2 tests, or >2 SD in 1 test. HAND was classified according to Frascati's criteria [8].

✓ **The VACS Index** was calculated through standard methods before starting DAA and 6 month after end of treatment. It included HIV biomarkers (CD4 cell count and HIV RNA), "non-HIV" biomarkers (hemoglobin, fib-4 - transaminases, platelets, age - creatinina clearance estimated by Modified Diet in Renal Disease - MDRD - and Hepatitis C serology), and age. HCV viremia was not included in the VACS Index calculation.

RESULTS 1

General results and characteristics of population are summarized in **Table 1** and **2**. Main results are shown in **figure 1, 2** and **3**: the histograms represent the proportions of neurocognitively impaired patients before and after DAA treatment, the box-plots display changes over time on NPZ8 and VACS Index, the scatter-plot shows the correlation between changes on NPZ8 and VACS Index.
Because of the high prevalence of confounding factors, mainly substance use, HAND diagnosis by Frascati's criteria was limited:

	ANI	MND	HAD
Before DAA (23 patients with NCI)	4 (6.4%)	1 (1.6%)	0
After DAA (26 patients with NCI)	2 (3.2%)	0	0

The VACS Index

Age (years)	< 50	0
	50-64	12
	> 64	27
CD4 (cells/mmc)	> 500	0
	350-499	6
	200-349	6
	100-199	10
	50-99	28
HIV RNA (copies/ml)	< 50	29
	< 500	0
	500-99.999	7
	> 1 x 10^5	14
Hemoglobin (g/dl)	> 14	0
	12-14	10
	10-11,9	22
	< 10	38
FIB-4	< 1,45	0
	1,45-3,25	6
	> 3,25	25
eGFR (ml/min)	> 60	0
	45-59,9	6
	30-49,9	8
	< 30	26
HCV co-infection (serologic status)		5

RESULTS 2

Table 1. Characteristics of population

Total patients (n=62)	
Male, n. (%)	46 (74,2%)
Age (years), median (IQR)	54 (51-56)
Injection Drug Users	53 (85.4%)
Hepatic fibrosis (Metavir stage)	
F1-F2	11 (17.7%)
F3	12 (19.3%)
F4	39 (62.9%)
HCV-RNA log, median (IQR)	5.8 (5.3-6.3)
HCV treatment	
experienced	31 (50.0%)
naive	31 (50.0%)
DAA regimen	
Sofosbuvir-based	
sofosbuvir + ribavirin +/- PegINF	15 (24.2%)
sofosbuvir+simeprevir +/- ribavirin	4 (6.5%)
sofosbuvir+daclatasvir +/- ribavirn	13 (21.0%)
sofosbuvir/ledipasvir +/-ribavirin	13 (21.0%)
2S/3D-based +/- ribavirin	17 (27.4%)
Duration	
12 weeks	34 (54.8%)
24 weeks	28 (45.2%)
HCV genotype	
1	4(6.5%)
1a	24 (38.7%)
1b	9 (14.5%)
2	1 (1.6%)
3	18 (29.0%)
4	6 (9.7%)

Figure 1. Proportion of patients with NCI before and after DAA

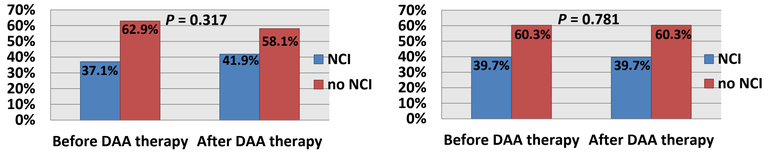


Figure 2. NPZ8 and VACS Index before and after DAA

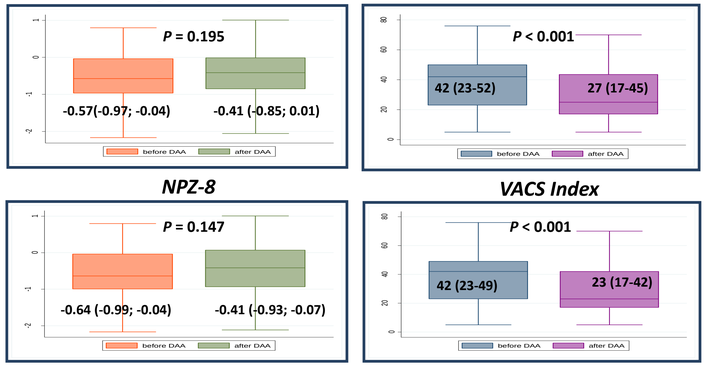
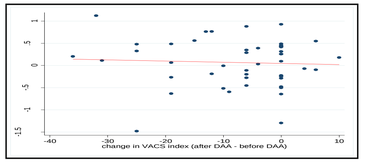


Figure 3. Correlation between changes in NPZ8 and VACS Index (n=62)



Spearman rho = 0.087 (p=0.530)

Table 2. Characteristics of population to calculate VACS Index

Total patients (n=62)		Before DAA	After DAA	P-value
HIV-RNA (copies/ml)	not detected	53 (85.5%)	55 (88.7%)	0.315
	<40	7 (11.3%)	5 (8.1%)	
	>=40	3 (4.8%)	2 (32%)	
CD4 count (cell/mmc), median (IQR)		563 (340-761)	554 (368-749)	0.179
Hemoglobin (g/dL), median (IQR)		**14.7 (14.0-15.8)**	**15 .0(14.3-15.6)**	**0.038**
ALT (UI/L), median (IQR)		**62 (38-80)**	**17 (13-27)**	**<0.001**
AST (UI/L), median (IQR)		**55 (32-84)**	**22 (18-28)**	**<0.001**
Platelet count (cell/mmc), median (IQR)		**136 (86-187)**	**152 (101-192)**	**0.020**
Fib-4		**2.9 (1.5-5.2)**	**2.0 (1.3-3.0)**	**<0.001**
Creatinine (mg/dl), median (IQR)		0.85(0.73-0.98)	0.83 (0.75-0.98)	0.802
eGFR (MDRD) (ml/min), median (IQR)		88 (70-102)	88 (73-105)	0.815

CONCLUSIONS

➢In our experience, DAA treatment strongly improved VACS Index, but did not impact on neurocognitive performance in HIV/HCV co-infected patients

➢These results could be explained by a poor contribution of HCV to neurocognitive impairment in HIV co-infected population

➢The elevated frequency of confounding factors in this highly vulnerable population may have masked benefit effect of DAA on neurocognition

➢Further studies , with a larger sample size and a longer follow up, are needed to better clarify the role of HCV on neurocognitive impairment.

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