HCV and Liver Disease Increase Risk of Neurocognitive Impairment in HIV+ Individuals

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Ilaria Mastrorosa, Carmela Pinnetti, Patrizia Lorenzini, Alessandra Vergori, Gabriele Fabbri, Pietro Balestra, Maria Maddalena Plazzi, Martina Ricottini, Rita Bellagamba, Stefania Cicalini, Rita Maddaluno, Mauro Zaccarelli, Adriana Ammassari, Andrea Antinori

National Institute for Infectious Diseases "Lazzaro Spallanzani", I.R.C.C.S., Rome, Italy

ABSTRACT

Background. HCV may be implicated in the pathogenesis of neurocognitive impairment (NCI), but its precise contribution in the setting of the HIV infected (HIV+) population is still controversial. HCV-mediated liver injury may itself contribute to NCI. We investigated the effect of HCV infection and liver function (Lf) on neurocognition.

Methods. From a prospective, monocenter, observational study conducted from January 2000 to July 2017 on neuropsychological (NP) evaluations, we selected HIV+ patients (pts) with known HCV status: negative serology (HCV-), positive serology (HCV+), viremic (RNA+), aviremic (RNA-). A comprehensive battery of 14 tests on 5 different domains was used to classify HIV-associated neurocognitive disorders (HAND) according to Frascati's criteria. NPZ8 was used as summary measure of z-scores of NP tests. Fibrosis 4 score (Fib4) was calculated as measure of Lf. Chi-square and K-Wallis tests were used for statistical comparisons. Stepwise backward multivariable logistic regression was employed to investigate predictors of HAND.

Results. Excluding pts with confounding factors for HAND diagnosis, we analyzed 1,305 pts: 953 HCV-, 109 HCV+RNA-, 243 HCV+RNA+. Male 79%, median age 45 yrs (IQR 38-52), median education 13 yrs (IQR 8-13), IDUs 17%, median CD4 nadir 215/mm3 (IQR 98-336) and current 491/mm3 (IQR 285-710), on antiretroviral therapy (ART) 82%, HIV RNA <50 copies/mL 59%. Table 1 depicts HAND prevalence and NPZ8 according to HCV status (1a) and to Fib4 score strata in all pts (1b) and in HCV+RNA+ pts (1c). A higher prevalence of HAND together with lower median NPZ8 scores were found in HCV+ pts (with or without HCV RNA) and with higher Fib4. In HCV+RNA+ pts, frequency of HAND was similar across Fib4 stages. Adjusting for demographics and clinical variables (age, education level, current and nadir CD4 count, HIV-RNA, mode of HIV transmission, years from HIV test, ART, Fib4), HCV+RNA+ was associated to higher risk of HAND [OR 1.51(1.06-2.13), p 0.021]. When excluding the variable age from the model, Fib4 >3.25 had higher risk of HAND [OR 2.04(1.15-3.61), p 0.015].

Conclusion. Our results show that both, HCV co-infection and worse liver function scores were associated with detrimental neurocognitive performance in HIV+ pts. Notably, among pts with actively replicating HCV, NCI was not in uenced by liver function scores. Now that curative anti-HCV therapy is available, these ndings need further investigation.

BACKGROUND and AIM

- Despite combination antiretroviral therapy (ART), Neurocognitive Impairment (NCI) remains an important comorbidity among HIV-infected persons and HIV-associated neurocognitive disorders (HAND) continue to occur in a substantial proportion of subjects[1].
- HCV may play a role in the neuropathogenetic pathway of NCI, but its precise contribution is still controversial in the setting of the HIV infected (HIV+) population[2]. While some studies suggested HCV replication in the CNS compartment[3] and an increased frequency of NCI[4] in HIV-infected subjects, other Authors showed no significant association of HCV infection as well as of HCV RNA level with NCI[5-6].
- Moreover, HCV-mediated liver injury may itself contribute to NCI.

***Aim** of the present analysis was to investigate the effect of both, HCV infection and liver function, on neurocognition.*

METHODS

From a single-center, prospective, observational study conducted from January 2000, at the HIV/AIDS Unit of the National Institute of Infectious Diseases "Lazzaro Spallanzani" in Rome, we selected patients with known HCV co-infection status and with a neuropsychological assessment (NPA) performed until July 2017.

- ✓ **NPA** was carried out through a standardized battery of 13 tests on 5 different domains*
- ✓ Subjects were classified as having HAND according to **Frascati's criteria**7**, excluding participants with confounding conditions likely to contribute to NCI
- ✓ We used **NPZ8** as a summary measure of z-scores of neuropsychological testing performance
- ✓ **HCV co-infection status** was so classified: negative serology (**HCV-**), positive serology (**HCV+**), viremic (**RNA+**), aviremic (**RNA-**)
- ✓ **Fibrosis 4 score** (**FIB4**) was calculated as measure of liver function
- ✓ Chi-square and K-Wallis tests were used for statistical comparisons. Stepwise backward multivariable logistic regression was employed to investigate predictors of HAND.

** concentration and speed of mental processing (Trail Making Test-A, WAIS-R Digit Symbol, Stroop color and word), mental flexibility (Trail Making Test-B, Stroop color-word, Controlled Oral Word-FAS, WAIS-R Digit Span backward), working memory (WAIS-R Digit Span forward and backward, Corsi's Block-Tapping Test), memory (RAVLT- Rey Auditory Verbal Learning Test, immediate and delayed recall) and fine motor functioning (Grooved Pegboard Test, dominant/non dominant hand)*

** Asymptomatic neurocognitive impairment (**ANI**): at least one standard deviation (SD) below the mean for norms in at least two cognitive domains, without interference in everyday functioning. Mild neurocognitive disorder (**MND**): as for ANI but with at least mild interference in daily functioning. HIV-associated dementia (**HAD**): at least two cognitive domains with a performance at least two SD below the mean for norms on neuropsychological test and with a marked interference in everyday functioning.

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CONTACT PERSON
Ilaria Mastrorosa, MD
National Institute for Infectious Diseases, I.R.C.C.S., "Lazzaro Spallanzani", Rome, Italy
Mail: *ilaria.mastrorosa@inmi.it*

RESULTS

Characteristics of population

Excluding patients with confounding factors for HAND diagnosis, we included 1,305 patients: 953 HCV-, 109 HCV+RNA-, 243 HCV+RNA+. General characteristics of all subjects at NPA are described in **Table 1**.

Table 1. Characteristics of population

Population (n=1305)		HCV- (n=953)	HCV+/RNA- (n=108)	HCV+/RNA+ (n=244)	*P*
Male gender, n (%)	1029 (78.9%)	767 (80.5%)	182 (74.9%)	80 (73.4%)	0,057
Age, median (IQR)	45 (38-52)	45 (37-53)	46 (41-53)	49 (43-54)	
Years of education, median (IQR)	13 (8-13)	13 (10-15)	11 (8-13)	10 (8-13)	<0.001
Years from HIV test, median (IQR)	6.5 (1.5-15)	4.3 (0.7-9.9)	13.7 (7.6-20.6)	16.8 (8.8-22.3)	<0.001
Mode of HIV transmission, n (%)					
homosexual	559 (42.8%)	508 (53.3%)	26 (23.8%)	25 (10.3%)	<0.001
Intravenous Drug User	215 (16.5%)	27 (2.8%)	36 (33.0%)	152 (62.5%)	
heterosexual	469 (35.9%)	366 (38.4%)	42 (38.5%)	61 (25.1%)	
other/unknown	62 (4.8%)	52 (5.5%)	5 (4.6%)	5 (2.1%)	
Nadir CD4+ cell/mm³, median (IQR)	215 (98-336)	232 (100-345)	198 (98-303)	180 (87-295)	0,003
Nadir CD4+ < 200 cell/mm³, n (%)	608 (46.6%)	418 (43.8%)	57 (52.3%)	133 (54.7%)	0,023
Current CD4+ cell/mm³, median (IQR)	491 (285-710)	507 (299-722)	456 (243-642)	480 (276-671)	0,078
Current CD4+ cell/mm³, n (%)					
< 350	414 (31.7%)	285 (29.9%)	45 (41.3%)	84 (34.6%)	0,269
351-500	247 (18.9%)	183 (19.2%)	16 (14.7%)	48 (19.7%)	
501-700	306 (23.4%)	223 (23.4%)	25 (22.9%)	58 (23.9%)	
> 701	336 (25.8%)	260 (27.3%)	23 (21.1%)	53 (21.8%)	
Current HIV RNA cp/ml, n (%)					
> 40	525 (40.2%)	393 (41.2%)	47 (43.1%)	85 (35.0%)	0,272
< 40	774 (59.3%)	557 (58.5%)	61 (56.0%)	156 (64.1%)	
On therapy, n (%)	1702 (82.4%)	775 (81.3%)	89 (81.7%)	211 (86.8%)	0,129
Off therapy, n (%)	230 (17.6%)	178 (18.7%)	20 (18.3%)	32 (13.2%)	
Type of ART regimen, n (%)					
NRTI + nNRTI	451 (34.6%)	370 (38.8%)	28 (25.7%)	53 (21.8%)	<0.001
NRTI + bPI	316 (24.2%)	214 (22.5%)	38 (34.9%)	64 (26.3%)	
NRTI + INSTI	54 (4.1%)	30 (3.1%)	3 (2.7%)	21 (8.6%)	
other	254 (19.5%)	161 (16.9%)	20 (18.3%)	73 (30.0%)	
FIB4, n (%)					
<1.45	754 (73.7%)	637 (82.2%)	41 (56.9%)	76 (43.2%)	<0.001
1.45-3.25	196 (19.2%)	114 (14.7%)	26 (36.1%)	56 (31.8%)	
>3.25	73 (7.1%)	24 (3.1%)	5 (6.9%)	44 (25.0%)	
Year of NPA, n (%)					
2000-2005	263 (20.1%)	160 (16.8%)	36 (33.0%)	67 (27.6%)	<0.001
2006-2011	485 (37.2%)	363 (38.1%)	43 (39.5%)	79 (32.5%)	
2012-2017	557 (42.7%)	430 (45.1%)	30 (27.5%)	97 (39.9%)	

HAND prevalence

Pie-chart shows HAND prevalence in all study population (**Figure 1**); the histograms depict frequency of HAND according to HCV co-infection status and FIB4 (**Figures 2a-c**).

Figure 1. HAND prevalence in all study population (n=1305)

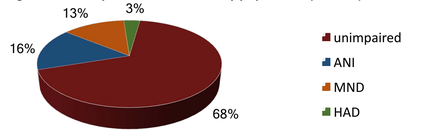


Figure 2a. HAND prevalence according to HCV co-infection status in all patients (n=1305)
***p* at *chi-square* < 0.001**

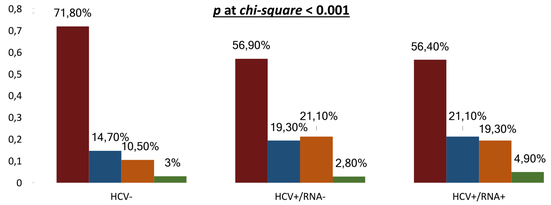


Figure 2b. HAND prevalence according to FIB4 in all patients (n=1305)
***p* at *chi-square* < 0.001**

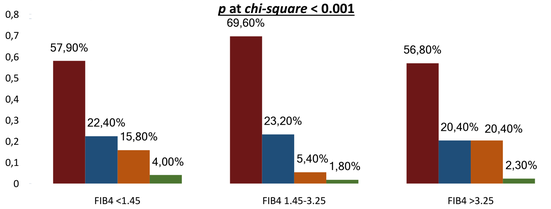
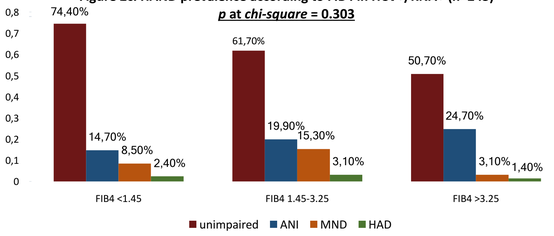
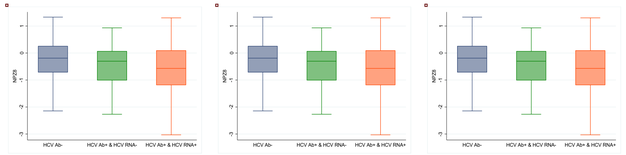


Figure 2c. HAND prevalence according to FIB4 in HCV+/RNA+ (n=243)
***p* at *chi-square* = 0.303**



NPZ8 score

Box plots represent median NPZ8 scores according to HCV co-infection status (**Figure 3a**) and to FIB4 score strata in all patients (**Figure 3b**) and in HCV+RNA+ patients (**Figure 3c**).



HAND predictors

The two tables below (**Table 2a-b**) show variables associated to HAND by ***stepwise backward multivariable logistic regressions***. The second model (**Table 2b**) does not consider the variable age, as it is already included in FIB4 score.

	OR	*CI 95%*		*P*
Age (per 10 years increase)	1,04	1,03	1,06	**<0,001**
Nadir CD4+ < 200 cell/mm³	1,70	1,25	2,31	**0,001**
Current HIV RNA cp/ml				
> 40	1,00			
< 40	0,76	0,52	1,10	0,148
undetectable	0,68	0,45	1,03	0,069
Current CD4+ cell/mm³				
< 350	1,00			
351-500	0,66	0,44	0,98	**0,042**
501-700	0,65	0,43	0,97	**0,037**
> 701	0,51	0,33	0,78	**0,002**
Education (per 1 year more)	0,85	0,81	0,88	**<0,001**
HCV co-infection status				
HCV-	1,00			
HCV+RNA-	1,34	0,85	2,13	0,211
HCV+RNA+	1,51	1,06	2,13	**0,021**
Type of ART regimen				
NRTI + nNRTI	1,00			
NRTI + bPI	1,06	0,74	1,51	0,767
NRTI + INSTI	0,26	0,11	0,60	**0,002**
other	0,76	0,51	1,13	0,176
no therapy	1,27	0,81	1,99	0,300
FIB4				
<1.45	1,00			
1.45-3.25	0,90	0,60	1,34	0,592
>3.25	1,41	0,77	2,58	0,272

Table 2a. Multivariable logistic regression

Table 2b. Multivariable logistic regression (age excluded)

	OR	*CI 95%*		*P*
Homosexual	0,78	0,59	1,04	0,091
Nadir CD4+ < 200 cell/mm³	1,75	1,29	2,36	**0,001**
Current CD4+ cell/mm³				
< 350	1,00			
351-500	0,63	0,43	0,93	**0,019**
501-700	0,62	0,42	0,91	**0,014**
> 701	0,47	0,32	0,71	**<0,001**
Education (per 1 year more)	0,84	0,80	0,87	**<0,001**
Type of ART regimen				
NRTI + nNRTI	1,00			
NRTI + bPI	1,11	0,78	1,57	0,555
NRTI + INSTI	**0,27**	**0,12**	**0,62**	**0,002**
other	0,78	0,52	1,15	0,204
no therapy	1,34	0,90	1,99	0,150
FIB4				
<1.45	1,00			
1.45-3.25	1,36	0,94	1,98	0,104
>3.25	**2,04**	**1,15**	**3,61**	**0,015**

CONCLUSIONS

- In our study, a higher prevalence of HAND together with lower median NPZ8 scores were found in individuals with HCV infection and with higher FIB4.
- When considering only patients with actively replicating HCV, NCI was not influenced by liver function scores; indeed, frequency of HAND was similar across FIB4 stages.
- Adjusting for other demographics and clinical variables, HCV co-infection and worse liver function scores confirmed the association with detrimental neurocognitive performance.
- Now that curative anti-HCV therapy is available, these findings need further investigation.