Infection (2013) 41:1103–1109
DOI 10.1007/s15010-013-0503-2

CLINICAL AND EPIDEMIOLOGICAL STUDY

Comparison of cognitive performance in HIV or HCV mono-infected and HIV–HCV co-infected patients

N. Ciccarelli · M. Fabbiani · P. Grima · K. Falasca · M. Tana · E. Baldonero · M. Colafigli · M. C. Silveri · J. Vecchiet · R. Cauda · S. Di Giambenedetto

Received: 24 February 2013 / Accepted: 25 June 2013 / Published online: 10 July 2013

Abstract
Purpose Our aim was to explore the interplay between human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections in the expression of cognitive disorders.
Methods We performed a multi-centre cross-sectional study, enrolling three groups of asymptomatic outpatients matched for age and education: (1) HIV mono-infected; (2) HCV mono-infected; (3) HIV–HCV co-infected. All subjects were subjected to the Zung depression scale and a comprehensive neuropsychological battery.
Results A total of 50 patients for each group were enrolled. Patients in the three groups did not significantly differ in the main common demographic and clinical characteristics, except for a lower proportion of past injecting drug use (IDU) in group 1 (4 %) in comparison to groups 2 (38 %, $p < 0.001$) and 3 (78 %, $p < 0.001$), a longer duration of HIV infection in group 3 in comparison to group 1 ($p < 0.001$) and a longer duration of HCV infection in group 3 in comparison to group 2 ($p = 0.028$). Overall, 39.3 % of patients showed minor cognitive impairment, with a higher proportion in group 3 (54 %) when compared to groups 1 (28 %, $p = 0.015$) or 2 (36 %, $p = 0.108$). Patients in group 3 [odds ratio (OR) 3.35, $p = 0.038$ when compared to group 1] and those with higher depression scores (OR 1.05, $p = 0.017$) showed an increased risk of cognitive impairment after adjusting for education and past injection drug use. In particular, group 3 showed worse performance in psychomotor speed tasks when compared to group 1 ($p = 0.033$).
Conclusions A worse cognitive performance in HIV–HCV co-infected patients was observed, suggesting an additive role of the two viruses in the pathogenesis of cognitive disorders.

Keywords HIV · HCV · Co-infection · Neuropsychological examination · Cognitive impairment

N. Ciccarelli · M. Fabbiani (✉) · E. Baldonero · M. Colafigli · R. Cauda · S. Di Giambenedetto
Institute of Clinical Infectious Diseases, Catholic University of Sacred Heart, Largo Agostino Gemelli 8, Rome 00168, Italy
e-mail: massifab@alice.it

N. Ciccarelli · E. Baldonero · M. C. Silveri
Memory Clinic, Catholic University of Sacred Heart, Largo Agostino Gemelli 8, Rome 00168, Italy

P. Grima · M. Tana
Division of Infectious Diseases, S. Caterina Novella Hospital, Via Roma, Galatina (Lecce) 73013, Italy

K. Falasca · J. Vecchiet
Infectious Diseases Clinic, University of Chieti, Via dei Vestini, Chieti 66100, Italy

Introduction

In the highly active antiretroviral therapy (HAART) era, despite dramatic changes in the natural history and prognosis of human immunodeficiency virus (HIV) infection, the incidence and prevalence of milder forms of HIV-associated neurocognitive disorders (HAND) have remained relatively stable [1, 2]. The sustained prevalence of HAND might be due to drug resistance, poor adherence, poor central nervous system (CNS) penetration of some antiretroviral agents [3] and the possible neurotoxicity of antiretrovirals on cognitive functions [4]. Moreover, there is growing evidence that underline co- morbidities as cardiovascular diseases [5, 6] and hepatitis C virus (HCV) co-infection could play a relevant role.

As a result of their shared routes of transmission, chronic HCV infection is increasingly recognised as a major cause of morbidity and mortality among HIV-infected patients. Recent US-based studies have shown that HCV co-infection may be found in 16–30 % of the HIV-infected population and in 60–90 % of HIV-infected injecting drug users [7]. Moreover, the prevalence of HCV infection is increasing around the world. It is estimated that HCV has infected 170 million people worldwide, whereas 34 million individuals are living with HIV [2, 8–11].

Patients with chronic HCV infection usually complain of fatigue and mild neuropsychological difficulties, including mental clouding ("brain frog") and subjective inability in everyday life. These complaints may be due to the effects of personality, the history of injecting drug use (IDU) or the presence of depression [12]. However, there is increasing evidence that cognitive dysfunctions might also be directly related to infection of the CNS by HCV. Indeed, HCV viral sequences and viral replicative forms have been detected in brain tissue [13] and it has been demonstrated that HCV can replicate in macrophages, lymphocytes and in peripheral nerves, especially in HIV-1-infected patients.

Until now, just a few studies have investigated cognitive functions among HCV-infected or HIV–HCV co-infected patients [11, 12, 14–16]. Overall, the results suggest an increased prevalence of neurocognitive impairment in HCV mono-infected patients than in healthy controls, and in HIV–HCV co-infected individuals when compared to HIV or HCV mono-infected patients, independently of the history of injection drug use, depression or fatigue, and before the development of cirrhosis. However, the effects of HCV on cognitive functioning remain controversial. Indeed, other results showed a similar prevalence of cognitive dysfunctions in the HIV–HCV co-infected group compared to HIV mono-infected patients [15, 17, 18]. Furthermore, previous studies differ for substantial methodological issues, including study design, neuropsychological tasks administered and methods for the estimation of cognitive disorders. In particular, HCV-infected patients are usually older, less educated and more frequently injecting drug users than HIV-positive patients, and some surveys did not control for these potential confounders in the interpretation of the results [14].

In our study, we compared cognitive performance in HIV or HCV mono-infected and HIV–HCV co-infected patients in order to better understand how HCV and HIV may interact in the expression of neurodegeneration, controlling for many potential confounding factors by matching 1:1:1 for age and education the three study groups.

Materials and methods

Patients

We performed a cross-sectional study at three clinical centres ("Agostino Gemelli" Hospital, Rome; "SS Annunziata" Hospital, Chieti; "S. Caterina Novella" Hospital, Galatina) in Italy, consecutively enrolling, from May 2010 to November 2011, three groups of asymptomatic (without active opportunistic infections or other acute clinical conditions) outpatients matched 1:1:1 for age (± 5 years) and years of education (primary school ≤5 years, secondary school from 6 to 8 years, high school from 9 to 16 years and university degree from 17 to 19 years): (1) HIV mono-infected; (2) HCV mono-infected; (3) HIV–HCV co-infected. HCV infection was defined as the positivity of anti-HCV antibodies with detectable HCV-RNA. Exclusion criteria were decompensated liver diseases or cirrhosis, history of neurologic disorders [including cerebral stroke, head injury and neurologic acquired immunodeficiency syndrome (AIDS)-defining events, with the exception of HIV-related dementia] and active psychiatric disorders (such as major depression or any other psychotic disorders), alcoholism or drug abuse, HCV treatment in the past 6 months and linguistic difficulties for non-native patients.

This study was approved by the local Institutional Ethics Committees at the three clinical centres. All subjects provided informed consent prior to enrollment.

Demographic, clinical and laboratory variables were collected for each subject at the time of neuropsychological examination by patient interview or chart review.

In patients infected by HIV (groups 1 and 3), a CNS penetration-effectiveness score (CPE rank) was calculated for each antiretroviral regimen based on the rules proposed in the 2010 revised version [19]. Regimens showing CPE rank ≥6 were considered as being effective in the treatment of CNS infection [20].

Neuropsychological examination

All patients underwent a comprehensive neuropsychological battery exploring memory [immediate and delayed recall of Rey auditory verbal learning test (RAVLT), forward digit span, forward spatial span], attention and executive functions (Stroop test, trail making test B, drawings and double barrage), speed of psychomotor processing (WAIS-R digit symbol; grooved pegboard test for both the dominant and non-dominant hand) and language (letter fluency). The Zung depression scale and the Instrumental Activities of Daily Living (IADL) scale were also administered.

Full testing took about 40 min. All tests were administered and scored by trained neuropsychologists. The scores obtained on each task were adjusted for age, gender and education on the basis of normative data available for the Italian population.

Patients were considered as mild cognitively impaired if they scored below the cut-off (1.0 SD below the mean for age–education-appropriate norms) in ≥3 tests on the basis of our previous data obtained in an age and education healthy control population [4] and according to standard criteria for composite neuropsychological battery [21]. We did not apply Frascati criteria [22] because they were established only for HIV-infected patients.

Because the three groups were matched for age and education, we also compared raw scores as continuous variables.

Statistical analysis

Comparisons between groups (three levels) were based on one-way analysis of variance (ANOVA, for continuous variables) and the χ^2 test or, when appropriate, Fisher's exact test (for categorical variables). The association between factors and cognitive impairment (dependent variable) was investigated by logistic regression analysis, while the association between factors and the total number of pathological performances (dependent variable) in any single cognitive domain (learning and long-term memory, attention and working memory, executive functions, speed of psychomotor processing and language) was analysed by linear regression analysis: variables with p-values lower than 0.100 in the univariate analysis were included in the multivariate models.

All analyses were performed using the SPSS version 13.0 software package (SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics

A total of 50 patients for each group ($n = 150$) [107 (71.3 %) males, median age 48 years (interquartile range, IQR 42–53), median education 10 years (IQR 8–13), 60 (40 %) past IDU] were enrolled. The predominant subtypes of HCV in groups 2 and 3 were genotypes 1 (48/100) and 3 (26/100).

Patients in the three groups did not significantly differ in the main common demographic and clinical characteristics, except for a lower proportion of past IDU in group 1 (4 %) in comparison to groups 2 (38 %, $p < 0.001$) and 3 (78 %, $p < 0.001$), a longer duration of HIV infection in group 3 in comparison to group 1 ($p < 0.001$), and a longer duration of HCV infection in group 3 in comparison to group 2 ($p = 0.028$). The demographic and clinical features for each group are shown in Table 1.

Neuropsychological examination

Overall, 39.3 % of patients showed mild cognitive impairment without significant interference in everyday life (IADL ≥7), with a higher proportion in group 3 (54 %) when compared to groups 1 (28 %, $p = 0.015$) or 2 (36 %, $p = 0.108$). Twenty patients (13.3 %) obtained an abnormal score (≥50) in the Zung depression scale. Raw scores for each task and comparison between the three groups by one-way ANOVA are illustrated in Table 2. Overall, group 3 had a significantly worse performance in comparison with group 1 at immediate and delayed RAVLT and letter fluency, while group 2 showed a lower performance compared with group 1 at delayed RAVLT, digit span forward and letter fluency. No significant difference was observed in the Zung depression scores.

Analysing the proportion of impairment (score below the normative cut-off) for each single task, the three groups did not significantly differ, with the exception of a higher proportion of subjects showing pathological scores in the WAIS-R digit symbol in group 3 (28 %) when compared to group 1 (10 %, $p = 0.040$).

Factors associated with cognitive impairment

Factors associated with neurocognitive impairment were identified by univariate and multivariate logistic regression analysis (Table 3). In the univariate analysis, patients in group 3 (odds ratio, OR 3.02, $p = 0.009$ when compared to group 1), those with past IDU (OR 2.10, $p = 0.030$) and with higher depression scores (OR 1.05, $p = 0.002$) showed an increased risk of cognitive impairment, while longer education (OR 0.78, $p < 0.001$) emerged as a protective factor.

In the multivariate analysis, patients in group 3 (OR 3.35, $p = 0.038$ when compared to group 1) and those with higher depression scores (OR 1.05, $p = 0.017$) confirmed an increased risk of cognitive impairment after adjusting for education and past IDU.

Analysing any single cognitive domain, group 3 showed worse performance in the psychomotor speed tasks when compared to group 1 ($p = 0.033$). No difference in the other domains was observed between groups (data not shown).

Table 1 Patient characteristics in human immunodeficiency virus (HIV) or hepatitis C virus (HCV) mono-infected and HIV–HCV co-infected patients

	HIV mono-infected (group 1) ($N = 50$)	HCV mono-infected (group 2) ($N = 50$)	HIV–HCV co-infected (group 3) ($N = 50$)
Male	32 (64)	36 (72)	39 (78)
Age (years)[a]	48 (42–55)	48 (42–52)	48 (45–53)
Education (years)[a]	10.50 (8–13)	10 (8–13)	9.50 (8–13)
Non-Italian born	2 (4)	0 (0)	0 (0)
Risk factor			
Heterosexual	27 (54)	0 (0)	6 (12)
Past injection drug user	2 (4)	19 (38)	39 (78)
Homosexual	16 (32)	0 (0)	0 (0)
Other	5 (10)	31 (62)	5 (10)
HBV co-infection	5 (10)	0 (0)	2 (4)
Past AIDS-defining events	10 (20)	–	9 (18)
Time from HIV diagnosis (years)[a]	11.4 (5.4–17.2)	–	16.3 (11.6–23.2)
Time on antiretroviral therapy (years)[a]	10.3 (5.5–12.5)	–	9.7 (5.4–12.6)
Off cART	6 (12)	–	3 (6)
HIV-RNA <50 copies/mL	41 (82)	–	40 (80)
Current CD4 cell count (cells/μL)[a]	571 (462–732)	–	468 (381–644)
Nadir CD4 cells count nadir (cells/μL)[a]	192 (70–260)	–	129 (59–251)
CPE rank ≥6	40 (80)	–	40 (80)
Time from HCV diagnosis (years)[a]	–	6.6 (2.6–12.5)	10.6 (7.5–12.5)
Past anti-HCV therapy	–	25 (50)	18 (36)
HCV-RNA ($\log_{10}$UI/L)[a]	–	5.73 (5.36–6.20)	6.1 (5.65–6.64)

Values are expressed as *n* (%), except for [a]median (interquartile range)

HCV hepatitis C virus, *HBV* hepatitis B virus, *cART* combined antiretroviral therapy, *CPE* central nervous system penetration-effectiveness score

Discussion

We conducted a comprehensive neuropsychological investigation comparing HIV or HCV mono-infected and HIV–HCV co-infected patients. Overall, 39.3 % of patients showed minor cognitive impairment, and the prevalence was significantly higher in HIV–HCV co-infected patients (54 %) than in mono-infected groups, suggesting an additive role of the two viruses in the pathogenesis of cognitive disorders. Furthermore, we observed only patients with minor cognitive impairment without interference in everyday life, probably because we enrolled only asymptomatic patients.

It is worthy to note that our results emerged in a study designed to control for frequent potential confounders observed when analysing the HCV-infected population. Indeed, we excluded patients with decompensated liver diseases or cirrhosis, active psychiatric disorders, alcoholism or drug abuse, and anti-HCV treatment in the past 6 months. Moreover, our groups were well matched for their social demographic status. Another strength of this study was that only patients with active HCV replication were included.

Previous data about the pattern of cognitive dysfunctions in HCV-infected patients, regardless of HIV infection, are inconsistent [12]. Our neuropsychological battery was comprehensive in order to explore a wide range of cognitive abilities. According to previous studies [11, 14, 23–25], we observed that co-infected patients had worse performance in long-term memory tasks and speed of mental information processing (WAIS-R digit symbol) compared to HIV or HCV mono-infected patients. It is worthy to note that we observed significant between-groups differences in only four neuropsychological tests. Probably, larger neuropsychological differences could have been highlighted by including subjects with a more severe cognitive disorder. Moreover, we did not observe different cognitive patterns between HIV or HCV mono-infected patients. As a consequence, on the basis of our data, it is not possible to formulate hypotheses about the specific effects of HIV or HCV per se on the CNS.

Depression is a common finding in HIV or HCV mono-infected and HIV–HCV co-infected patients, both as a secondary phenomenon to viral infections and because there is a high prevalence of mood disorders in the background of patients [12]. We did not observe differences between study groups in the depression scores. Nevertheless, depression confirmed an independent association with a higher risk of cognitive impairment [12, 26]. This finding underscores the negative impact of depression on HIV–HCV prognosis and highlights the need for interventions aimed at preventing or early treating mental disorders.

Table 2 Between-groups comparisons of neuropsychological performance in each task

	HIV mono-infected (group 1) ($N = 50$)	HCV mono-infected (group 2) ($N = 50$)	HIV–HCV co-infected (group 3) ($N = 50$)	p Value	Notes
Immediate RAVLT	43.00 (9.83)	40.58 (8.86)	37.48 (10.84)	**0.022**	Group 1 vs. 3, $p =$ **0.006**
Delayed RAVLT	9.2 (3.30)	8.00 (2.64)	7.50 (3.39)	**0.019**	Group 1 vs. 2, $p =$ **0.049**
					Group 1 vs. 3, $p =$ **0.006**
Digit span (forward)	5.94 (1.25)	5.32 (0.82)	5.56 (1.24)	**0.023**	Group 1 vs. 2, $p =$ **0.007**
Spatial span (forward)	4.92 (1.07)	4.98 (0.85)	5.08 (1.03)	0.714	
Stroop test (errors)	1.44 (2.45)	2.16 (2.87)	1.27 (1.73)	0.147	
Stroop test (time)	19.86 (8.30)	20.82 (11.88)	19.42 (8.47)	0.767	
Trail making test B (errors)	0.58 (1.13)	0.74 (1.08)	0.90 (1.33)	0.404	
Trail making test B (time)	137.46 (65.96)	155.10 (59.07)	166.72 (109.11)	0.196	
Drawings	4.40 (1.06)	4.38 (1.73)	4.67 (1.78)	0.672	
Letter fluency	34.90 (11.63)	28.14 (9.24)	30.39 (11.15)	**0.007**	Group 1 vs. 2 $p =$ **0.002**
					Group 1 vs. 3 $p =$ **0.039**
WAIS-R digit symbol	8.69 (2.09)	7.78 (1.96)	7.94 (2.55)	0.095	
Double barrage	0.95 (0.76)	0.97 (0.31)	0.95 (0.80)	0.360	
Pegboard (dominant hand)	73.40 (19.48)	75.21 (16.29)	79.13 (17.88)	0.284	
Pegboard (non-dominant hand)	79.63 (27.98)	79.01 (18.40)	83.50 (23.22)	0.603	
Number of pathological tasks	2.04 (1.88)	2.54 (2.70)	3.12 (2.55)	0.083	
Zung depression score	35.06 (10.89)	36.56 (10.71)	38.94 (10.06)	0.187	

Raw scores for each task are expressed as mean (standard deviation). Significant p values are in **bold**

As expected, a higher level of education confirmed an independent association with cognitive performance, probably because a major "cognitive reserve" modulates the detrimental effects of HIV or HCV diseases on cognitive abilities [27, 28].

In our study, variables related to the severity of the HIV or HCV infections, such as current and nadir CD4 cell count and plasma HIV or HCV viral load, were not associated with neuropsychological performance. One possible explanation for this finding could be that our cohort included only asymptomatic patients. Moreover, we did not observe any association between CPE rank and cognitive abilities, probably because of the great heterogeneity in the patients' medical histories and biases due to the small size of the study samples or to the cross-sectional study design. Furthermore, suboptimal adherence, together with possible drug resistance mutations compartmentalised into the CNS, could be other potential explanations for our finding [20, 29]. Until now, studies evaluating the relationship between CPE and cognitive performance have reported controversial results [30]. We acknowledge that our study can have some limitations because uncontrolled biases can occur in cross-sectional surveys performed in routine clinical practice. We did not control for a lower proportion of past IDU in HIV mono-infected patients than in HCV mono-infected or HIV–HCV co-infected groups. However, in the current epidemiological situation, it can be very difficult to enroll a large number of HCV-infected patients without a history of illicit drugs use. Anyway, in the multivariate analysis, patients with HIV–HCV co-infection confirmed a higher risk for cognitive impairment after adjusting for past IDU. Furthermore, we did not collect data about sleep disorders, fatigue, quality of life and anxiety, which are common symptoms in HIV- and HCV-infected patients, and which might have a negative impact on cognitive abilities [12]. Moreover, our sample size was relatively small, thus, potentially influencing the statistical power of the analysis and the representativeness of the population (even if patients were consecutively enrolled during outpatient visits). However, other studies investigating a similar topic also enrolled a comparable number of subjects (ranging from 64 to 264) [11, 14, 17], since, in routine clinical practice, it could be very difficult to test larger populations with a comprehensive neuropsychological battery.

Finally, the lack of a healthy uninfected subjects group has prevented better exploration of whether HIV and HCV are additive or interactive factors in the expression of cognitive disorders. Thus, additional controlled longitudinal studies are needed in order to confirm our findings and to discriminate direct consequences of HIV and HCV on the CNS from effects related to associated factors.

In conclusion, our study showed a higher risk of neuropsychological deficits in a population of HIV–HCV co-infected patients, independent of depression, past IDU and social demographic variables. Monitoring the cognitive status in patients with co-morbidities and multiple risk factors for the development of neuropsychological dysfunction could help clinicians to early diagnose and manage cognitive impairment in HIV- and/or HCV-infected patients.

Table 3 Factors associated with cognitive impairment

	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	*p* Value	OR (95 % CI)	*p* Value
Variables explored in the total population				
Sex (male vs. female)	0.86 (0.42–1.77)	0.688		
Age	1.01 (0.97–1.06)	0.544		–
Education (per 1 year more)	0.78 (0.69–0.89)	**<0.001**	0.78 (0.68–0.89)	**<0.001**
Past injection drug users	2.10 (1.07–4.12)	**0.030**	0.83 (0.32–2.14)	0.698
Zung depression scale (per 1 point more)	1.054 (1.02–1.09)	**0.002**	1.05 (1.01–1.08)	**0.017**
Groups				
HIV mono-infected	**1 (ref)**		**1 (ref)**	
HCV mono-infected	1.45 (0.62–3.37)	0.392	1.37 (0.51–3.66)	0.528
HIV–HCV co-infected	3.02 (1.32–6.93)	**0.009**	3.35 (1.07–10.52)	**0.038**
Variables explored in the total HIV population (groups 1 and 3)				
Duration of HIV infection (per 1 year longer)	1.04 (0.98–1.10)	0.166		
Time on antiretroviral therapy (per 1 year longer)	1.03 (0.93–1.13)	0.594		
Past AIDS-defining events	1.79 (0.66–4.90)	0.256		
HIV-RNA <50 copies/mL	1.24 (0.44–3.48)	0.683		
CD4 cells count nadir	0.10 (0.1–1.00)	0.129		
CD4 cells count	0.10 (0.1–1.00)	0.154		
CPE rank ≥6	1.37 (0.49–3.81)	0.543		
Variables explored in the total HCV population (groups 2 and 3)				
Duration of HCV infection	1.07 (0.98–1.16)	0.124		
HCV-RNA (log_{10}UI/L)	1.255 (0.88–1.78)	0.205		

Acknowledgements No specific funding was received for this study.

Conflict of interest M.F. received speakers' honoraria from Abbott Virology, Merck Sharp & Dohme and Janssen-Cilag. K.F. received speakers' honoraria from Bristol-Myers Squibb. M.C. has been a paid consultant for Merck Sharp & Dohme, Italy and was employed by Bristol-Myers-Squibb, Italy from May 10th, 2010 to February 28th 2011. M.C.S. received travel grants from Novartis and Lundbeck, and research support from the Catholic University of Rome. J.V. received speakers' honoraria from Gilead, Bristol-Myers Squibb, Abbott, Janssen-Cilag and ViiV. R.C. has been an advisor for Gilead and Janssen-Cilag, received speakers' honoraria from ViiV, Bristol-Myers Squibb, Merck Sharp & Dohme and Janssen-Cilag, and research support from "Fondazione Roma". S.D.G. received speakers' honoraria and support for travel to meetings from Gilead, Bristol-Myers Squibb, Abbott, Boehringer Ingelheim, Janssen-Cilag and GlaxoSmithKline. The other authors have nothing to declare.

References

1. McArthur JC. HIV dementia: an evolving disease. J Neuroimmunol. 2004;157:3–10.
2. UNAIDS. AIDS epidemic update 2009. Available at: http://www.unaids.org/en/media/unaids/contentassets/dataimport/pub/report/2009/jc1700_epi_update_2009_en.pdf. Accessed 7 July 2013.
3. Cysique LA, Brew BJ. Neuropsychological functioning and antiretroviral treatment in HIV/AIDS: a review. Neuropsychol Rev. 2009;19:169–85.
4. Ciccarelli N, Fabbiani M, Di Giambenedetto S, Fanti I, Baldonero E, Bracciale L, et al. Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. Neurology. 2011;76:1403–9.
5. Fabbiani M, Ciccarelli N, Tana M, Farina S, Baldonero E, Di Cristo V, et al. Cardiovascular risk factors and carotid intima-media thickness are associated with lower cognitive performance in HIV-infected patients. HIV Med. 2013;14:136–44.
6. Sacktor N, Skolasky R, Selnes OA, Watters M, Poff P, Shiramizu B, et al. Neuropsychological test profile differences between young and old human immunodeficiency virus-positive individuals. J Neurovirol. 2007;13:203–9.
7. Sherman KE, Rouster SD, Chung RT, Rajicic N. Hepatitis C Virus prevalence among patients infected with Human Immunodeficiency Virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. Clin Infect Dis. 2002;34:831–7.
8. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med. 2001;345:41–52.
9. Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected patient. Clin Liver Dis. 2003;7:179–94.
10. Caudai C, Maimone D, Almi P, Annunziata P, Bastianoni I, Boggiano CA, et al. The potential role of hepatitis C virus in the pathogenesis of the neurological syndrome in chronic hepatitis C. Gut. 1997;41:411–2.
11. Clifford DB, Evans SR, Yang Y, Gulick RM. The neuropsychological and neurological impact of hepatitis C virus co-infection in HIV-infected subjects. AIDS. 2005;19:S64–71.
12. Forton DM, Allsop JM, Cox IJ, Hamilton G, Wesnes K, Thomas HC, et al. A review of cognitive impairment and cerebral metabolite abnormalities in patients with hepatitis C infection. AIDS. 2005;19:S53–63.

13. Letendre S, Paulino AD, Rockenstein E, Adame A, Crews L, Cherner M, et al. Pathogenesis of hepatitis C virus coinfection in the brains of patients infected with HIV. J Infect Dis. 2007;196:361–70.
14. Richardson JL, Nowicki M, Danley K, Martin EM, Cohen MH, Gonzalez R, et al. Neuropsychological functioning in a cohort of HIV- and hepatitis C virus-infected women. AIDS. 2005;19:1659–67.
15. Vivithanaporn P, Nelles K, DeBlock L, Newman SC, Gill MJ, Power C. Hepatitis C virus co-infection increases neurocognitive impairment severity and risk of death in treated HIV/AIDS. J Neurol Sci. 2012;312:45–51.
16. Hilsabeck RC, Perry W, Hassanein TI. Neuropsychological impairment in patients with chronic hepatitis C. Hepatology. 2002;35:440–6.
17. Thein H, Maruff P, Krahn M, Kaldor J, Koorey DJ, Brew B, et al. Cognitive function, mood and health-related quality of life in hepatitis C virus (HCV)-monoinfected and HIV/HCV-coinfected individuals commencing HCV treatment. HIV Med. 2007;8:192–202.
18. Heaton RK, Cysique LA, Jin H, Shi C, Yu X, Letendre S, et al. Neurobehavioral effects of human immunodeficiency virus infection among former plasma donors in rural China. J Neurovirol. 2008;14:536–49.
19. Letendre S, Ellis R, Deutsch R, Clifford D, Marra C, McCutchan A, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER cohort. In: 17th Conference on Retroviruses and Opportunistic Infections (CROI); San Francisco, California, February 2010.
20. Ciccarelli N, Fabbiani M, Colafigli M, Trecarichi EM, Silveri MC, Cauda R, et al. Revised central nervous system neuropenetration-effectiveness score is associated with cognitive disorders in HIV-infected patients with controlled plasma viraemia. Antivir Ther. 2013;18:153–60.
21. Capitani E, Laiacona M. Composite neuropsychological batteries and demographic correction: standardization based on equivalent scores, with a review of published data. The Italian Group for the Neuropsychological Study of Ageing. J Clin Exp Neuropsychol. 1997;19:795–809.
22. Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007;69:1789–99.
23. Kramer L, Bauer E, Funk G, Hofer H, Jessner W, Steindl-Munda P, et al. Subclinical impairment of brain function in chronic hepatitis C infection. J Hepatol. 2002;37:349–54.
24. Forton DM, Taylor-Robinson SD, Thomas HC. Cerebral dysfunction in chronic hepatitis C infection. J Viral Hepat. 2003;10:81–6.
25. Forton DM, Thomas HC, Murphy CA, Allsop JM, Foster GR, Main J, et al. Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. Hepatology. 2002;35:433–9.
26. Ammassari A, Antinori A, Aloisi MS, Trotta MP, Murri R, Bartoli L, et al. Depressive symptoms, neurocognitive impairment, and adherence to highly active antiretroviral therapy among HIV-infected persons. Psychosomatics. 2004;45:394–402.
27. Stern RA, Silva SG, Chaisson N, Evans DL. Influence of cognitive reserve on neuropsychological functioning in asymptomatic human immunodeficiency virus-1 infection. Arch Neurol. 1996;53:148–53.
28. Bieliauskas LA, Back-Madruga C, Lindsay KL, Wright EC, Kronfol Z, Lok AS, et al. Cognitive reserve and neuropsychological functioning in patients infected with hepatitis C. J Int Neuropsychol Soc. 2007;13:687–92.
29. Canestri A, Lescure FX, Jaureguiberry S, Moulignier A, Amiel C, Marcelin AG, et al. Discordance between cerebral spinal fluid and plasma HIV replication in patients with neurological symptoms who are receiving suppressive antiretroviral therapy. Clin Infect Dis. 2010;50:773–8.
30. Cavassini M, Du Pasquier RA. A light in the cognitive fog? Antivir Ther. 2013;18:149–51.