Published in final edited form as:
Neurology. 2004 March 23; 62(6): 957–962.

Neuropsychiatric impact of hepatitis C on advanced HIV

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Abstract

Objective—To determine whether hepatitis C (HCV) contributes to CNS dysfunction among HIV-infected individuals.

Methods—Using a cross-sectional design, the neuropsychiatric profile of individuals with advanced HIV coinfected with hepatitis C (HIV+/HCV+) was compared to similarly advanced HIV patients without HCV coinfection (HIV+/HCV−). Participants were derived from the Manhattan HIV Brain Bank and underwent neurocognitive testing and semistructured psychiatric interviews. Evidence of HCV infection was determined by serology performed prior to study entry. Hepatic function was determined by serum chemistries (bilirubin, creatinine, and international normalized ratio) at the time of the cognitive assessments.

Results—Coinfected (HIV+/HCV+) individuals were significantly more likely to have had past opiate or cocaine or stimulant dependence. HIV+/HCV+ participants also had significantly greater rates of past substance-induced major depression. There were no significant differences in rates of primary mental disorders. Forty-two percent of both the HIV+/HCV+ and HIV+/HCV− participants met criteria for current major depression. There was a trend for HIV+/HCV+ patients to perform worse neurocognitively. On tests of executive functioning, HIV+/HCV+ individuals exhibited a greater rate of impairment and had significantly more perseveration. Differences in cognitive functioning were associated with serology but did not correlate with indices of liver disease severity. The HCV+ patients were also more likely to be diagnosed with HIV-associated dementia.

Conclusions—There appears to be a neuropsychiatric impact of HCV that is detectable even among an advanced HIV cohort.

Highly active antiretroviral therapy (HAART) has largely transformed HIV/AIDS from a fatal to a chronic illness, thus allowing the emergence of significant comorbidities to impact CNS function. Hepatitis C (HCV)–related liver disease is now a leading cause of morbidity and mortality in HIV-infected individuals.[1,2] Both HIV and HCV are bloodborne pathogens that can result in a subclinical, chronic stage of infection. Each is resistant to eradication through present available treatments and has extraordinarily high replication rates with billions of HIV virions and trillions of HCV virions produced daily.[3] Risk factors common to both diseases, especially parenteral drug use, contribute to the high rate of coinfection of HIV and HCV. The prevalence of HCV among HIV-positive individuals is estimated to be 30%[4,5] and among injection drug users, 70 to 90%.[5,6] HIV and HCV both affect CNS functioning and are associated with cognitive dysfunction.[7,8]

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Supported by grant R24MH59724 (to S.M.) and the Clinical Research Center of the Mount Sinai School of Medicine (M01-RR-00071) from the NIH.

Using a cross-sectional design, the present study compared the neuropsychiatric profiles of HIV+/HCV+ coinfected individuals with HIV+ infected patients without HCV. We determined the prevalence of neuropsychiatric disorders among an advanced HAART-era AIDS cohort coinfected with HCV, and assessed whether the presence of the two viruses was related to greater neuropsychiatric compromise. We tested the hypothesis that the HCV+ participants would display greater rates of depression and cognitive impairment and raise the possibility that coinfection may result in detectable synergy even in advanced stages of HIV.

Methods

Subjects

Study participants were derived from Manhattan HIV Brain Bank (MHBB) enrolled patients who had laboratory documentation of HCV antibody status prior to study entry. All MHBB participants are HIV-positive and give consent for anatomic gift enabling postmortem organ donation for research purposes. Further MHBB participation eligibility criteria include 1) advanced HIV disease or another disease without effective therapy (indicator conditions include progressive multifocal leukoencephalopathy, lymphoma [systemic or CNS], disseminated mycobacteriumavium-intercellulare, wasting [>30% of lean body mass], AIDS dementia complex, cytomegalovirus end organ disease, viscera Kaposi sarcoma, congestive heart failure, or serum albumin <3.2 g/dL); 2) a CD4 count ≤50 cells/mm^3 for at least a 3-month period of time; or 3) substantive risk for imminent mortality in the judgment of the participant's primary physician. Upon recruitment, all participants undergo a series of neurologic, neuropsychologic, and psychiatric examinations. General medical information and antiretroviral histories are obtained through participant interview and chart review.

Laboratory values

HCV antibody status, current CD4, and HIV plasma RNA were obtained from medical records. Serum albumin was collected at the assessment. For each participant, we also calculated a Model for End Stage Liver Disease (MELD) score,[9] an accurate predictor of mortality risk used to assesses the severity of liver disease and state of hepatic compensation. MELD scores (MELD score = [0.957 * Log_e(creatinine mg/dL) + 0.378 * Log_e(bilirubin mg/dL) + 1.12 * Log_e(INR) + 0.643] * 10) range from 6 (less ill) to 40 (gravely ill) and are computed from serum bilirubin, creatinine, and international normalized ratio (INR) values. Scores <12 are consistent with compensated hepatic function. Urine toxicology was collected at the time of the neuropsychological assessment except when logistic or medical reasons (i.e., end stage renal disease) prohibited collection. The HIV+/HCV− participants were significantly more likely to have a positive toxicology screen for an illicit substance. Methadone was considered a prescribed substance. Overall, 19 participants screened positive for cocaine with or without another illicit non-opiate drug, 8 participants had opiates (2 with opiates and benzodiazepines), and 6 participants had cocaine and opiates. The remaining participants screened positive for cannabis, benzodiazepines, barbiturates, or a combination of these.

Psychiatric interview

The Psychiatric Research Interview for Substance and Mental Disorders (PRISM)[10] is administered to each participant to obtain psychiatric and substance use histories. The PRISM targets the comorbidity of substance use disorders and mental disorders such that primary mental disorders can be differentiated from substance-induced syndromes and from the expected effects of intoxication and withdrawal. The PRISM assesses current diagnostic status (within the last 12 months) and past history (previous 12 months).

Neuropsychological battery

Participants are administered a battery of neuropsychological (NP) tests that assess a broad range of cognitive abilities including psychomotor speed, attention, memory, verbal fluency, executive function, and premorbid cognitive functioning. Specific tests included the Trailmaking Test–Parts A and B (TMT-A and TMT-B),[11] Grooved Pegboard Test–Dominant and Nondominant Hands (GPT-DH and GPT-NDH),[12,13] Hopkins Verbal Learning Test (HVLT),[14] Brief Visual Memory Test–Revised (BVMT-R),[15] Digit Symbol, Symbol Search, Letter Number Sequencing,[16] Controlled Oral Word Association Test (FAS),[17] Wisconsin Card Sorting Test–64 card version (WCST-64),[18] and the Reading subtest of the Wide Range Achievement Test-3 (WRAT-3).[19] The individual tests were also grouped according to the following domains: motor—GPT-DH, GPT-NDH; psychomotor speed—TMT-A, Digit Symbol, Symbol Search; working memory—Letter Number Sequencing, Paced Auditory Serial Addition Task (PASAT); learning—HVLT Total Recall, BVMT-R Total Recall; memory—HVLT Delayed Recall, BVMT-R Delayed Recall; verbal fluency—FAS; executive functioning—WCST-64 Perseverative Responses and TMT-B. To investigate prevalence of impairment across domains, we assigned *t*-scores using the following published norms: GPT-DH, GPT-NDH, TMT-A, TMT-B,[20] FAS,[21] Digit Symbol, Symbol Search, Letter Number Sequencing,[16] BVMT-R,[15] PASAT,[22] HVLT,[14] and WCST-64.[18] A global *t*-score was assigned based on the mean of all the tests in the battery.

Neurologic examination

Participants underwent a standard neurologic examination conducted by a board certified neurologist.

Instrumental activities of daily living

The Instrumental Activity of Daily Living Scale (IADLS)[23] was used.

Cognitive disorders

Participants were classified according to a modified American Academy of Neurology (AAN) algorithm.[24] For a diagnosis of HIV-1-associated dementia complex (ADC), a participant must 1) score 1 SD below age- and education-adjusted norms on 2 of 10 neuropsychological tests (TMT-A, TMT-B, HVLT, BVMT, WCST-64, COWAT, Digit Symbol, Symbol Search, Letter Number Sequencing, PASAT) or 2 SD below the norms on 1 of 10 tests and 2) have difficulty (due to either a physical or cognitive deficit) in one of the following IADL/ADL: using the phone, handling money, taking medication, performing housekeeping, doing laundry, preparing meals, grocery shopping, driving or using public transportation, understanding reading materials/television, making minor home repairs, working, childcare, bathing, or dressing. They must also meet one or two of the following: 1) any impairment in lower extremity strength, coordination, leg agility, or performance on grooved pegboard (dominant hand) 2 SD below mean and 2) depression that interferes with function, loss of interest in usual activities, or emotional lability.

A diagnosis of HIV-associated minor cognitive/motor disorder (MCMD) was made when participants did not meet criteria for ADC and met the following criteria: 1) deficit in at least two of the following: mental slowing—Digit Symbol, TMT-A, or Symbol Search 1 SD below age and education-adjusted norms; memory—HVLT or BVMT-R total learning or delayed recall at least 1 SD below norms; motor dysfunction—impairment in GPT-DH 1 SD below norms; incoordination—impairment in coordination or gait; emotional lability or apathy/withdrawal; and 2) deficit in at least one role function measure attributed in part to a cognitive function: fatigue that interferes with activities, limited in work or activities, difficulty performing activities, or requires special assistance.

Data analysis

For each analysis, we compared the two patient groups (HIV+/HCV+ and HIV+/HCV−). All NP tests were administered and scored according to standardized procedures. Unless otherwise specified raw scores were used in data analysis, and skewed scores were log transformed. Transformed scores did not change the results so we present untransformed scores in all the tables. We examined the prevalence of impairment by converting raw scores to standard scores based on published norms and then using χ^2 analyses. Impairment was defined as ≤1.5 SD below the mean (or a *t*-score of ≤ 35).

Results

Subject information

The sample included 67 HIV+/HCV+ participants and 49 HIV+/HCV− participants (table 1). Mean age was 43.7 years and mean education was 12 years. HCV+ participants were significantly older. There were no significant differences in sex between the HCV+ and HCV − groups. There were also no significant differences in reading raw scores, an index of premorbid intelligence.

Substance use disorders and primary mental disorders

Rates of substance use disorders are shown in table 2. HIV+/HCV+ participants were more likely to have had a past history of opiate dependence ($\chi^2 = 31.18$, $p < 0.01$) or cocaine dependence ($\chi^2 = 4.22$, $p < 0.05$) or stimulant dependence ($\chi^2 = 5.43$, $p < 0.05$). There were no significant differences in past or current substance abuse diagnoses. Rates of substance abuse diagnoses ranged from 0 to 7% and were much lower than substance dependence, except for past cannabis abuse for which approximately one-quarter of both the HIV+/HCV+ and HIV+/HCV− groups met the criteria. Substance-induced disorders were uncommon; substance-induced major depression was the most prevalent syndrome with significantly more HIV+/HCV+ participants meeting criteria for this disorder. There were no significant differences in the rates of primary mental disorders (table 3). Past and current depression were the most common diagnoses in both groups. Past dysthymia, past post-traumatic stress disorder, and childhood conduct disorder were the next most commonly occurring disorders. No participant had past or current hypomania, obsessive-compulsive disorder, hallucinations or delusions, schizophrenia, schizophreniform disorder, schizoaffective disorder, psychotic mood disorder, or depression due to a secondary general medical condition.

Neuropsychological impairment of HCV+ participants

Means and SD of NP test scores for both groups are shown in table 4. Individual neuropsychological tests are grouped by domain. There was an overall trend for the HIV+/HCV− group to perform better. Stepwise multiple regression revealed that the HIV+/HCV+ group exhibited more perseverative responses on WCST and coinfection was a predictor of perseveration whereas age and opiate dependence were not (adjusted $R^2 = 0.037$; $F_{1,105} = 5.03$, $p < 0.05$). No differences were found on NP tests among those with and without past dependence of opiates, cocaine, or stimulants. Participants with a positive illicit toxicology screen scored significantly lower only on visual memory (BVMT-R Delayed Recall).

Prevalence of impaired neuropsychological functioning

There was a high level of impairment in the motor, learning, and memory domains with greater than half of the participants in each group scoring 1.5 SD below the mean. Overall, impairment rates were roughly equivalent across domains with the exception of executive functioning (table 5). Forty-three percent of HCV+ participants versus 29% of HCV− participants scored

≤1.5 SD below the mean on the executive functioning domain (which is the mean *t*-score of performance on TMT-B and WCST Perseverative Responses based on published norms).

Relationship between liver disease severity and neuropsychological performance

MELD scores were available for 82 participants. There was no significant difference in MELD scores between the two groups (see table 1); serum albumin was also equivalent. The MELD scores were not significantly associated with any of the cognitive tests. None of the coinfected patients exhibited asterixis on the neurologic examination. Review of available autopsies revealed nine patients had cirrhosis at autopsy: 47% (7/15) were coinfected patients whereas only 17% (2/12) of the HCV− patients had cirrhosis. MELD scores as well as serum albumin were equivalent for the autopsy groups. There was also no difference in overall NP impairment or executive functioning between the autopsy-verified cirrhotic and non-cirrhotic patients.

Prevalence of neurocognitive disorders

Participants were assigned neurocognitive diagnoses based on a modification of the AAN algorithm.[24] Participants with a report of learning disability or head injury with sustained (>30 minutes) loss of consciousness were assigned NP impairment—Other. Significantly more HIV +/HCV+ participants (46% versus 10%) met criteria for ADC and significantly more HIV+/ HCV− participants (45% versus 23%) met criteria for MCMD (table 6). Neuropsychological impairment, depression, motor strength or coordination difficulties, and the number of ADL complaints were entered separately into a regression to predict neurocognitive diagnosis. Logistic regression revealed that greater severity of NP impairment predicted ADC (OR 0.90; 90% CI 0.82, 0.99) such that those with greater deviation from normal NP functioning were more likely to receive a diagnosis of ADC.

Functional ability

Although there were no significant differences in IADL/ADL complaints between the two groups, both groups had compromised functional ability. The MELD scores were also not associated with IADL/ADL complaints.

Discussion

HIV has been shown to have a significant neuropsychiatric impact. There have been a myriad of pre-HAART era studies documenting neurocognitive and psychiatric effects of HIV.[7,25–27] In general these studies reveal that advanced symptomatic patients exhibit greater rates of impairment.[28] The correlation of cognitive impairment with advanced HIV disease persists in the HAART era. While the severity of dementia has lessened, its existence remains. Recently, a large autopsy series showed increased incidence of mild to moderate encephalopathy from the pre-AZT to the HAART era[29] revealing a direct effect of HIV on the brain despite HAART. Thus, the longevity afforded to patients by HAART may make them susceptible to progressive CNS disease. For example, the median CD4 count at ADC diagnosis appears to be increasing[30] although the disorder is still most apparent in populations with CD4 ≤ 200. In the HAART era, ADC appears to be evolving from a disorder of rapid deterioration to a more insidious and chronic condition. Our cohort, the MHBB, with advanced AIDS and a mean CD4 count of 168 (SD = 17), is thus a population at risk for cognitive dysfunction.

HCV as well as liver disease has also been associated with significant neuropsychiatric dysfunction. Neurocognitively, HCV-infected patients exhibit decrements in sustained attention, psychomotor speed, and set-shifting.[8,31,32] Although one study[8] was unable to differentiate an effect of HCV from other chronic liver diseases, another[31] demonstrated that HCV viremia in the absence of cirrhosis or significant fibrosis was associated with cognitive impairment. Furthermore, these deficits (i.e., working memory and concentration deficits) were

independent of IV drug use history, depression, or fatigue. Another study[33] also found neurometabolic elevations of choline/creatine in basal ganglia and white matter in patients with histologically mild HCV. Thus, there is evidence of a cerebral effect of HCV even in the absence of liver failure and resulting hepatic encephalopathy.

Whether cognitive effects seen in HCV individuals are due to CNS viral penetration of HCV is unclear. The data regarding extrahepatic replication of HCV are controversial with some studies not finding evidence of replication.[34,35] Recently, there has been preliminary evidence that HCV can replicate at extrahepatic sites particularly under conditions of immunodeficiency. Among HIV patients, HCV has been detected in lymph and peripheral blood mononuclear cells (PBMC), suggesting that HCV is lymphotropic in vivo under conditions of impaired immunity.[36] Most recently, replicative forms of HCV were detected in the CNS that were more closely related to viral strains in PBMC than in serum.[37–39] Thus, it appears that HCV-infected leukocytes can carry the virus into the CNS where viral replication may be sustained in an independent compartment. Replication could be facilitated by immunosuppression as replicative forms of HCV are commonly found in HIV-coinfected patients or liver transplant recipient patients[40,41] and rarely found in PBMC from normal subjects.[34,42] In addition to the possible extrahepatic manifestations of HCV, decompensated liver functioning may result in cognitive dysfunction (hepatic encephalopathy or minimal hepatic encephalopathy) either through reduced extraction and metabolism of encephalopathic substances or portosystemic shunting.[43] Either phenomenon or the combined effect of both could potentiate neuropsychiatric impairment in coinfected individuals and may affect different anatomic (basal ganglia versus cortical) and cellular (astrocytic versus macrophage) compartments.

Regardless of mechanism, the MHBB cohort, with 61% having HCV antibodies, is at high risk for HCV-related CNS dysfunction. HCV replication in monocytes/macrophages and also in T and B lymphocytes has been documented in HIV-infected patients, and there is indication that HCV may replicate in the same cells as HIV thereby potentially causing direct interactions between the two viruses.[37] The neuropsychological impairment reported among HCV patients is similar to that of HIV-infected patients with both affecting cognitive domains subserved by frontal-subcortical circuits.

Preliminary studies indicate a neuropsychiatric impact of HCV/HIV coinfection. In a small sample, coinfected individuals (n = 14) were more likely to show overall cognitive impairment than patients with exclusively HIV (n = 58) or HCV (n = 19).[44] In our study, we see evidence of neurocognitive effects of coinfection in an advanced HIV cohort without significant hepatic decompensation. There was a trend for the coinfected group to perform worse neurocognitively. In addition to greater rates of impairment, we also found significantly more perseveration among the coinfected patients. Our ability to detect greater impairment is surprising given that HIV and HCV appear to have similar patterns of neurocognitive disruption and advanced HIV is associated with significant cognitive decline. Further investigation of executive functioning among coinfected individuals with an earlier stage of HIV infection may elucidate whether executive functioning is differentially affected by coinfection. The significant burden of HIV in our cohort may mask the HCV contribution to cognitive dysfunction. Finally, HCV+ patients in our sample were more likely to meet criteria for ADC and thus appear to have a more severe neurocognitive disorder despite similar HIV (CD4 and RNA plasma level) and liver disease (MELD) indices.

Although there appears to be a neuropsychiatric impact of HCV, future studies with indicators of HCV disease severity (HCV RNA load and fibrosis stage) as well as a broader spectrum of HIV disease may help clarify the pattern and extent of CNS dysfunction.

Acknowledgements

The authors thank the patients and staff of the Manhattan HIV Brain Bank. Investigators and staff of the Manhattan HIV Brain Bank include the following: Laurie Abromowitz, CSW; Sherly Altidor, PA; Laura Banks, MD; Yvonne Brown, RN; Jacqueline Crittendon, BS; Alessandro DiRocco, MD; David Dorfman, PhD; Colleen Dowling, RN; Lydia Estanislao, MD; Yan Ling Gao, MD; Anthony Geraci, MD; Tauseef Haider, MD; Deborah Hesketh, RN; Talha Idrees, MD; Geraldine Joseph, PA; Shafat Khan, MD; Victoria Kozlowski, RN; Damien Laudier, BS; Rashid Mahboob, MD; Lalitha Mantha, RN; Aleks Maryanchik, MS; Natalie Massenberg, BS; Letty Mintz, ANP; Christine Mondragon, RN; Jennifer Monzones, BA; Jacinta Murray, BS; Daniel Polowetsky, RN; Phyllis Ristau, RN; Monica Rivera Mindt, PhD; Amy Scarano, BS; Victoria Sharp, MD; David Simpson, MD; JoAnne Sweeney, RN; Michele Tagliati, MD; Susama Verma, MD; Milana Veytsman, BS; Enrique Wulff, MD; Tatiana Yakoushina, MD; and Mohammad Zaidi, MD.

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Table 1

Demographic and clinical characteristics of HCV+ and HCV− participants

Variable	HCV+, n = 67	HCV−, n = 49	*p* Value
Age, y	45.1 (7.2)	41.9 (7.2)	0.05
Education, y	12.3 (2.3)	11.8 (3.4)	0.35
WRAT-3 reading	39.4 (8.9)	40.1 (8.7)	0.67
CD4	164.7 (171.2)	141.8 (206.6)	0.59
Log plasma HIV RNA	3.7 (1.6)	4.1 (1.5)	0.29
MELD	8.0 (2.1)	7.7 (2.3)	0.47
Sex			0.59
Men	49	38	
Women	18	11	
Ethnicity			0.65
African American	30	20	
White	15	10	
Hispanic	22	18	
Asian	0	1	
Tox screen positive*	18	21	0.03

Values are mean (SD) or n.

* Not all subjects received a urine toxicology screen because of logistic and medical reasons (i.e., end stage renal disease).

HCV = hepatitis C; WRAT = Wide Range Achievement Test; MELD = Model for End Stage Liver Disease.

Table 2

Substance related disorders, %

Substance use disorders	HCV+, n = 62	HCV−, n = 45	*p* Value
Alcohol dependence, P	47	51	0.66
Alcohol dependence, C	10	16	0.36
Cannabis dependence, P	19	22	0.71
Cannabis dependence, C	3	7	0.41
Cocaine dependence, P	73	53	0.04
Cocaine dependence, C	16	24	0.29
Opiate dependence, P	81	27	0.00
Opiate dependence, C	13	4	0.14
Hallucinogen dependence, P	11	4	0.21
Hallucinogen dependence, C	2	0	0.39
Sedative dependence, P	13	4	0.14
Sedative dependence, C	3	0	0.22
Stimulant dependence, P	11	0	0.02
Stimulant dependence, C	2	0	0.39
Other dependence, P	3	0	0.22
Other dependence, C	2	0	0.39
Substance-induced depression, P	6	0	0.03
Substance-induced depression, C	1	0	0.39

HCV = hepatitis C; P = past, >12 months ago; C = current, within the last 12 months.

Table 3

Primary mental disorders, %

Primary mental disorder	HCV+, n = 62	HCV−, n = 45	*p* Value
Primary depression, P	71	62	0.34
Primary depression, C	42	42	0.98
Dysthymia, P	19	16	0.61
Dysthymia, C	3	2	0.76
Mania, P	2	0	0.39
Mania, C	2	0	0.39
PTSD, P	19	18	0.84
PTSD, C	8	11	0.59
Childhood conduct disorder	16	18	0.82
ASPD since age 15	15	13	0.86
ASPD, C	0	4	0.09
BPD, P	7	9	0.64
BPD, C	7	7	0.97
Panic, P	3	2	0.76
Panic, C	2	2	0.82
GAD, P	11	4	0.21
GAD, C	10	2	0.12

HCV = hepatitis C; P = past, >12 months ago; C = current, within the last 12 months; PTSD = post-traumatic stress disorder; ASPD = antisocial personality disorder; BPD = bipolar disorder; GAD = generalized anxiety disorder.

Table 4

Mean (SD) neuropsychological (NP) test scores by group

NP domain	HCV+, n = 67	HCV−, n = 49	*p* Value
Motor			
Grooved Pegboard–DH (s)	95.0 (30.1)	91.7 (34.1)	0.62
Grooved Pegboard–NDH (s)	111.4 (41.3)	99.3 (29.4)	0.08
Psychomotor speed			
TMT-A (s)	48.6 (18.4)	45.9 (19.1)	0.45
Digit Symbol	46.3 (14.6)	47.8 (17.2)	0.63
Symbol Search	21.6 (7.6)	22.3 (9.0)	0.69
Working Memory			
Letter Number Sequencing	8.0 (3.0)	8.0 (2.2)	0.91
PASAT	25.4 (10.6)	24.6 (10.1)	0.76
Learning			
HVLT Total Recall	19.5 (5.8)	21.0 (4.7)	0.12
BVMT Total Recall	13.9 (7.5)	15.5 (7.1)	0.26
Memory			
HVLT Delayed Recall	6.2 (3.0)	6.2 (2.5)	0.99
BVMT Delayed Recall	5.2 (3.0)	5.7 (3.0)	0.38
Verbal Fluency			
FAS	31.4 (12.9)	29.5 (10.2)	0.38
Executive Functioning			
TMT-B (s)	143.7 (83.0)	123.6 (66.9)	0.16
WCST Perseverative Responses	24.1 (17.7)	16.3 (11.5)	0.006

HCV = hepatitis C; DH = dominant hand; NDH = nondominant hand; TMT = Trailmaking Test; PASAT = Paced Auditory Serial Addition Task; HVLT = Hopkins Verbal Learning Test; BVMT = Brief Visual Memory Test; WCST = Wisconsin Card Sorting Test.

Table 5

Prevalence of impaired neuropsychological (NP) performance

NP domain	HCV+, n = 67	HCV−, n = 49	*p* Value
Global	55	53	0.82
Motor	61	63	0.82
Psychomotor speed	44	43	0.92
Working memory	35	33	0.86
Learning	71	68	0.72
Memory	72	69	0.72
Verbal fluency	32	28	0.65
Executive functioning	43	29	0.13

Values are percentages.

HCV = hepatitis C.

Table 6

Prevalence of neurocognitive disorders

Neurocognitive diagnosis	HCV+, n = 26	HCV−, n = 29	*p* Value
Normal	4	10	0.29
NP impairment–other	27	35	0.55
MCMD	23	45	0.02
ADC	46	10	0.003

Values are percentages.

HCV = hepatitis C; MCMD = minor cognitive/motor disorder; ADC = HIV-1-associated dementia complex.