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Authors

Clifford, David B

Vaida, Florin

Kao, Yu-Ting

et al.

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Absence of neurocognitive effect of hepatitis C infection in HIV-coinfected people

David B. Clifford, MD
Florin Vaida, PhD
Yu-Ting Kao, MS
Donald R. Franklin, BS
Scott L. Letendre, MD
Ann C. Collier, MD
Christina M. Marra, MD
Benjamin B. Gelman, MD, PhD
Justin C. McArthur, MBBS
Susan Morgello, MD
David M. Simpson, MD
Igor Grant, MD
Robert K. Heaton, PhD
For the CHARTER Group

Correspondence to
Dr. Clifford:
cliffordd@wustl.edu

ABSTRACT

Objective: To investigate the effect of hepatitis C virus (HCV) on neurocognitive performance in chronically HIV-infected patients enrolled in the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study.

Methods: A total of 1,582 participants in CHARTER who were tested for HCV antibody underwent neurocognitive testing; serum HCV RNA was available for 346 seropositive patients. Neurocognitive performance was compared in 408 HCV-seropositive and 1,174 HCV-seronegative participants and in a subset of 160 seropositive and 707 seronegative participants without serious comorbid neurologic conditions that might impair neurocognitive performance, using linear regression and taking into account HIV-associated and demographic factors (including IV drug use) and liver function.

Results: Neurocognitive performance characterized by global deficit scores and the proportion of individuals who were impaired were the same in the HCV-seropositive and HCV-seronegative groups. In univariable analyses in the entire sample, only verbal domain scores showed small statistically different superior performance in the HCV+ group that was not evident in multivariable analysis. In the subgroup without significant comorbidities, scores in all 7 domains of neurocognitive functioning did not differ by HCV serostatus. Among the HCV-seropositive participants, there was no association between neurocognitive performance and serum HCV RNA concentration.

Conclusion: In HIV-infected patients, HCV coinfection does not contribute to neurocognitive impairment, at least in the absence of substantial HCV-associated liver damage, which was not evident in our cohort. *Neurology* 2015;84:241–250

GLOSSARY

APRI = AST to platelet ratio index; **CHARTER** = CNS HIV Antiretroviral Therapy Effects Research; **CLIA** = Clinical Laboratory Improvement Amendments; **FIB4** = fibrosis 4 index; **GDS** = global deficit scores; **HAND** = HIV-associated neurocognitive disorders; **HCV** = hepatitis C virus; **MELD** = Model for End-stage Liver Disease; **NP** = neuropsychological; **WRAT-3** = Wide Range Achievement Test–oral reading score.

Hepatitis C virus (HCV) infection is a worldwide problem that is often linked to HIV infection. At least 170 million people worldwide are infected with HCV, while an estimated 33 million worldwide are infected with HIV.[1] Coinfection most commonly occurs in individuals who use IV drugs. In the United States, approximately 30% of HIV-infected patients are coinfected with HCV.[2]

Neurocognitive impairment is a prevalent complication of HIV infection, with 40%–50% of HIV-infected (HIV+) patients performing below expectations on quantitative neurocognitive tests.[3] The reasons for continued prevalence of cognitive impairment are not understood, especially since contributions of HIV virus have been significantly reduced by successful antiretroviral treatments. Neural injury occurring before HIV treatment initiation, toxicity of antiretroviral therapy, ongoing low-level CNS inflammation with neurologic damage, or comorbid conditions may all contribute to persistent impairment.[4,5]

Supplemental data
at Neurology.org

HCV has been implicated as a cause of neurocognitive or neurobehavioral impairment.[6–9] However, studies to determine the precise contribution of HCV to cognitive impairment in the setting of HIV coinfection have been limited by lack of appropriate controls, cohorts with modest sample size, and limited evaluations of neuropsychological (NP) or neurocognitive status. Moreover, HCV-mediated liver injury or adverse effects of interferon-based treatment used for HCV can themselves cause cognitive impairment. As a result, the current literature reflects conflicting opinions as to whether HCV constitutes an independent risk for cognitive abnormalities in HIV.[10–19] The issue of whether HCV contributes significantly to HIV-associated neurocognitive impairments may be especially important now because more successful and tolerable curative therapy for HCV is rapidly emerging.[20]

METHODS **Subjects.** The CNS HIV Antiretroviral Therapy Effects Research (CHARTER) cohort consists of 1,582 HIV+ participants who were roughly evenly drawn from 6 participating university centers: Johns Hopkins University (Baltimore, Maryland, n = 231); Mt. Sinai School of Medicine (New York, n = 270); University of California at San Diego (n = 289); University of Texas Medical Branch (Galveston, n = 261); University of Washington (Seattle, n = 262); and Washington University (St. Louis, Missouri, n = 269).[21,22]

Standard protocol approvals, registrations, and patient consents. Assessments carried out in this contracted research were designed by the CHARTER leadership working collaboratively with officials from the supporting NIH institutes. These procedures were approved by the Human Subjects Protection Committees of each participant's institution.

Procedures. As previously described for the CHARTER study methods, for baseline assessment, all subjects completed a neuromedical assessment, comprehensive NP testing, detailed substance use history, structured psychiatric interviews for detecting lifetime and current diagnoses of substance use disorders and affective disorders, a measure of current mood, and self-report assessments of cognitive symptoms, vocational functioning, and independence with instrumental activities of daily living.[21] For further details of the CHARTER study methods, see reference 21 or visit the CHARTER Web site (https://www.charterresource.ucsd.edu).

Neuromedical examination. Neuromedical examination included medical history, structured neurologic and medical examination, and collection of blood and urine samples. For those who consented (n = 1,205), CSF was obtained by lumbar puncture. These procedures were performed by physicians, nurse practitioners, or trained nurses and research associates under the supervision of site investigators, after central standardization of the procedure by the coordinating center.

Laboratory assessment. HIV infection was diagnosed by ELISA with Western blot confirmation. Routine clinical chemistry panels

(electrolytes, glucose, blood urea nitrogen, creatinine, hepatic transaminases, bilirubin), complete blood counts (total leukocyte count, hemoglobin, hematocrit, platelets), rapid plasma reagin, HCV antibody, and CD4+ T cells (flow cytometry) were performed at each site's Clinical Laboratory Improvement Amendments (CLIA)–certified (or CLIA-equivalent) laboratory. HIV RNA levels were measured centrally in plasma and CSF by reverse transcriptase PCR (Roche [Basel, Switzerland] Amplicor, v 1.5, lower limit of quantitation 50 copies/mL). Roche COBAS AmpliPrep/COBAS TaqMan HCV test was used for measuring HCV RNA in serum specimens that had been stored at −8°C. This test has a lower detection limit of approximately 10 IU/mL and a linear amplification range of HCV RNA from 43 to 69,000,000 IU/mL.

Neurobehavioral examination. All participants completed a comprehensive NP test battery, covering 7 major cognitive domains known to be commonly affected by HIV-associated CNS dysfunction (administration time = 2–2.5 hours).[21] The best available normative standards were used, which convert raw scores to standardized T scores that correct for effects of age, education, sex, and ethnicity, as appropriate. We applied a clinical rating algorithm for classifying presence and severity of overall neurocognitive impairment. This highly structured classification system conforms to Frascati criteria for HIV-associated neurocognitive disorders (HAND) diagnoses, and yields high interrater reliability in multisite HIV studies.[23–26] T scores were also converted into deficit scores according to the following criteria: ≥40 T = 0; 39 T–35 T = 1; 34 T–30 T = 2; 29 T–25 T = 3; 24 T–20 T = 4; and ≤19 T = 5. The deficit scores were then averaged to derive domain and global deficit scores (GDS) for each participant.[23]

Classification of comorbid conditions. Identifying HAND requires that the neurocognitive impairment and functional disability are due to effects of HIV on the brain, and not solely to comorbid conditions. "This determination requires not only detailed information about the comorbid conditions themselves, but also clinical judgment about their severity, their likely effect on neurocognition and everyday functioning, their timing in relation to the course of HIV disease and any functional limitations in everyday life."[21]

To facilitate interrater reliability of these determinations, we used the online supplement to the report by Antinori et al.,[25] which provides detailed guidelines for classifying the most commonly encountered comorbid conditions as incidental, contributing, or confounding.[21] Incidental conditions are those that may affect neurocognitive performance to a slight degree, but would be unlikely (by themselves) to cause the person to be classified as significantly impaired. Given the uncertainty surrounding HCV infection and cognition, this alone did not constitute a reason to disqualify categorization in the incidental group. Thus, HCV+ participants could qualify for the lowest or incidental comorbid risk category where there would be minimal other confounding factors beyond HIV. Contributing conditions "could cause at least mild neurocognitive impairment, but the severity, nature or timing of the impairment and associated disability make it likely that the currently observed impairment and functional decline also represent significant effects of HIV."[3] Confounding conditions are believed to be sufficient to explain observed NP impairment and currently observed problems with everyday functioning. Analysis for HCV effects was done in both the incidental group, where an isolated interaction with HIV would be most likely to be detected, and the entire cohort, so as to use all available comparisons with the entire population of HCV+ participants.

Variable	HCV− (n = 1,174)		HCV+ (n = 408)		p Value
	No.	Mean ± SD or n (%)	No.	Mean ± SD or n (%)	
Age[a]	1,174	42.1 ± 8.8	408	45.9 ± 6.8	<0.001[b]
Education[a]	1,174	12.9 ± 2.6	408	11.5 ± 2.2	<0.001[b]
WRAT scaled score[a]	1,163	93.5 ± 16	405	85.5 ± 16.4	<0.001[b]
Male sex[c]	1,174	926 (78.9)	408	290 (71.1)	0.0017[b]
Comorbidity[c]					
Incidental	1,174	707 (60.2)	408	160 (39.2)	<0.001[b]
Contributing		307 (26.1)		169 (41.4)	
Confounding		160 (13.6)		79 (19.4)	
Ethnicity[c]					
African American	1,172	497 (42.4)	408	262 (64.2)	<0.001[b]
Hispanic		122 (10.4)		27 (6.6)	
Caucasian		518 (44.2)		115 (28.2)	
Other		34 (3)		4 (1)	
Site[c]					
University of Washington	1,174	200 (76.3)	408	62 (23.7)	<0.001[b]
Washington University		241 (89.6)		28 (10.4)	
UTMB		183 (70.1)		78 (29.9)	
JHU		114 (49.4)		117 (50.6)	
MSSM		188 (69.6)		82 (30.4)	
UCSD		248 (85.8)		41 (14.2)	
% IV drug use[c]	1,174	111 (9.5)	408	207 (50.7)	<0.001[b]
% IV as primary route of drug use[c]	1,174	73 (6.2)	408	200 (49)	<0.001[b]
% IV drug use, ever[c]	1,174	158 (13.5)	408	273 (66.9)	<0.001[b]
% IV drug use, composite[c,d]	1,174	180 (15.3)	408	294 (72.1)	<0.001[b]
Duration of HIV infection, y[a]	1,163	9.3 ± 6.5	403	11.7 ± 5.8	<0.001[b]
Current CD4[a]	1,164	463 ± 284.2	404	463.5 ± 299	0.97
Nadir CD4[a]	1,174	215.5 ± 193.4	408	193.8 ± 201.1	0.053
% AIDS[c]	1,174	705 (60.1)	408	285 (69.9)	<0.001[b]
Log_{10} HIV RNA: plasma[a]	1,155	2.9 ± 1.32	403	2.79 ± 1.3	0.18
Log_{10} HIV RNA: CSF[a]	907	2.19 ± 0.84	321	2.13 ± 0.8	0.21
% Detectable HIV RNA: plasma[c]	1,155	703 (60.9)	403	225 (55.8)	0.077
ART status[c]					
% On ART	1,174	817 (69.9)	408	294 (70.1)	0.26
% ART naive		203 (17.3)		54 (13.2)	
% Off ART (prior ART only)		154 (13.1)		60 (14.7)	
% Employed[c]	1,173	365 (31.1)	408	60 (14.7)	<0.001[b]
% IADL dependent[c]	1,077	204 (18.9)	372	83 (22.3)	0.17
Beck Depression Inventory-II score[a]	1,171	13.9 ± 10.5	408	14.2 ± 11.7	0.58
% Reporting moderate-severe fatigue[c,e]	1,171	213 (18.2)	408	85 (20.8)	0.24
AST SGOT[a]	1,170	34.2 ± 25.5	404	56.8 ± 48.7	<0.001[b]
ALT SGPT[a]	1,170	37.3 ± 30.2	404	62.8 ± 68.7	<0.001[b]
ALT ≥60[c]	1,170	145 (12.4)	404	151 (37.4)	<0.001[b]
Log_{10} HCV RNA: serum[a,f]	118	1.45 ± 0	346	5.29 ± 1.98	<0.001[b]

	HCV− (n = 1,174)		HCV+ (n = 408)		
Variable	No.	Mean ± SD or n (%)	No.	Mean ± SD or n (%)	p Value
MELD[a]	1,142	1.49 ± 2.49; 0.91 (0–21.77)[g]	391	1.77 ± 4.67; 0.36 (0–44.26)[g]	0.42
APRI[a]	1,165	0.17 ± 0.23	403	0.31 ± 0.38	<0.001[b]
APRI, by range[c]					
≤0.5	1,165	1,128 (96.8)	403	350 (86.8)	<0.001[b]
0.5–1.5		31 (2.7)		47 (11.7)	
≥1.5		6 (0.5)		6 (1.5)	
FIB4[a]	1,165	1.2 ± 1.1	403	1.8 ± 1.5	<0.001[b]
FIB4, by range[c]					
0–1	1,165	1,072 (92)	403	291 (72.2)	<0.001[b]
2–3		75 (6.4)		90 (22.3)	
≥4		18 (1.5)		22 (5.5)	

Abbreviations: ALT = alanine aminotransferase; APRI = aspartate transaminase to platelet ratio index; ART = antiretroviral therapy; AST = aspartate transaminase; FIB4 = fibrosis 4 score; HCV = hepatitis C virus; IADL = instrumental activities of daily living; JHU = Johns Hopkins University; MELD = Model for End-stage Liver Disease score; MSSM = Mt. Sinai School of Medicine; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; UCSD = University of California at San Diego; UTMB = University of Texas Medical Branch; WRAT = Wide Range Achievement Test.

[a] Mean ± SD; comparison using t test, unless otherwise noted.
[b] Significant.
[c] No. (%); comparison using Fisher exact test.
[d] IV drug use, composite: coded as yes if any of the IV drug use variables are yes.
[e] Based on item 20, "tiredness or fatigue," of Beck Depression Inventory, second edition.
[f] HCV RNA values were eliminated for 21 patients who are HCV− but HCV RNA detectable, $\log_{10}$ HCV RNA: serum >1.4473.
[g] Median (range); comparison using Wilcoxon rank-sum test.

Statistical methods. The demographic and clinical characteristics of the participants were compared between the HCV+ and HCV− groups using the independent-samples t test for the continuous variables and Fisher exact test for binary and categorical variables. The Model for End-stage Liver Disease (MELD) scores and Beck Depression Inventory were compared between groups using Wilcoxon rank-sum test due to the highly skewed distribution.

The domain-specific NP scores and GDS were compared between the HCV+ and HCV− groups using linear regression in unadjusted and adjusted analyses. Three adjusted models were performed, controlling for the following potential confounders and important predictors of neurocognitive impairment: (1) log10 plasma HIV RNA, self-reported nadir CD4, Wide Range Achievement Test–oral reading score (WRAT-3), years of education, ethnicity, comorbidity category, and duration of known HIV infection; (2) covariates in model 1 and 4 variables defining IV drug exposure in the population (tables 1 and 2); (3) covariates in model 2 and liver function markers: aspartate aminotransferase, alanine aminotransferase, MELD, AST to platelet ratio index (APRI), and fibrosis 4 index (FIB4). In addition, the unadjusted and 3 adjusted models with the predictors listed above comparing clinical rating impairments between HCV+ and HCV− groups were performed using logistic regression.

Among the HCV-seropositive group, analysis of neurocognitive outcomes, domain-specific NP scores and global deficit scores, and HCV RNA concentration in serum was performed using linear regression.

RESULTS Demographics. The characteristics of the 1,582 HIV infected individuals who underwent NP and HCV antibody testing are shown in table 1. The characteristics of the 867 subjects with only minimal comorbidities are shown in table 2. Coinfected patients were older, were less educated, and had lower WRAT-3 reading scores, and they were more likely to be female and African American than those not infected with HCV. A much higher proportion of HCV+ participants used IV drugs, reflecting the predominant transmission pattern for HCV. The HCV+ coinfected group was also less likely to be employed. There were no significant group differences in self-reported depressed mood or significant fatigue.[27] As expected, serum hepatic transaminase concentrations were significantly higher in the HCV+ coinfected group. However, the extent of liver damage was minimal. The MELD scores were similar for HCV-seropositive and HCV-seronegative participants. While numerically higher in the HCV+ coinfected group, the APRI was consistent with liver fibrosis (APRI > 1.5) in only one HCV+ and 2 HCV− patients in the incidental cohort (table 2). Similarly, the FIB4 index

Table 2	Demographic and clinical association of the incidental comorbidity group, with moderately and severely confounded individuals excluded				
	HCV− (n = 707)		HCV+ (n = 160)		
Variable	No.	Mean ± SD or n (%)	No.	Mean ± SD or n (%)	p Value
Age[a]	707	41.6 ± 9.2	160	46.3 ± 6.1	<0.001[b]
Education[a]	707	13.3 ± 2.5	160	11.8 ± 2.3	<0.001[b]
WRAT scaled score[a]	703	97.2 ± 14	159	88.5 ± 15.1	<0.001[b]
Male sex[c]	707	572 (80.9)	160	117 (73.1)	0.031[b]
Ethnicity[c]					
African American	706	276 (39.1)	160	107 (66.9)	<0.001[b]
Hispanic		67 (9.5)		13 (8.1)	
Caucasian		348 (49.3)		39 (24.4)	
Other		14 (2.1)		1 (0.6)	
Site[c]					
University of Washington	707	114 (83.2)	160	23 (16.8)	<0.001[b]
Washington University		125 (93.3)		9 (6.7)	
UTMB		114 (80.3)		28 (19.7)	
JHU		56 (56.6)		43 (43.4)	
MSSM		114 (75)		38 (25)	
UCSD		184 (90.6)		19 (9.4)	
% IV drug use[c]	707	58 (8.2)	160	82 (51.2)	<0.001[b]
% IV as primary route of drug use[c]	707	38 (5.4)	160	80 (50)	<0.001[b]
% IV drug use, ever[c]	707	91 (12.9)	160	107 (66.9)	<0.001[b]
% IV drug use, composite[c,d]	707	101 (14.3)	160	113 (70.6)	<0.001[b]
Duration of HIV infection, y[a]	700	8.9 ± 6.6	158	12 ± 5.7	<0.001[b]
Current CD4[a]	704	473.6 ± 279	159	462 ± 293.9	0.64
Nadir CD4[a]	707	229.6 ± 199	160	187.5 ± 212.6	0.017[b]
% AIDS[c]	707	394 (55.7)	160	118 (73.8)	<0.001[b]
Log_{10} HIV RNA: plasma[a]	692	2.93 ± 1.32	159	2.78 ± 1.24	0.17
Log_{10} HIV RNA: CSF[a]	548	2.24 ± 0.85	123	2.08 ± 0.75	0.055
% Detectable HIV RNA: plasma[c]	692	427 (61.7)	159	91 (57.2)	0.32
ART status[c]					
% On ART	707	474 (67.0)	160	118 (73.8)	0.097
% ART naive	707	145 (20.5)	160	20 (12.5)	
% Off ART (prior ART only)	707	88 (12.5)	160	22 (13.7)	
% Employed[c]	707	267 (37.8)	160	32 (20)	<0.001[b]
% IADL dependent[c]	663	105 (15.8)	144	24 (16.7)	0.80
AST SGOT[a]	704	32.3 ± 18.4	158	55.2 ± 31.5	<0.001[b]
Beck Depression Inventory-II score[a]	704	12.3 ± 9.7	160	11.8 ± 10.9	0.59
% Reporting moderate-severe fatigue[c,e]	704	97 (13.8)	160	27 (16.9)	0.31
ALT SGPT[a]	704	36.6 ± 24.3	158	61.5 ± 41.7	<0.001[b]
ALT ≥60[c]	704	85 (12.1)	158	66 (41.8)	<0.001[b]
Log_{10} HCV RNA: serum[a,f]	68	1.45 ± 0	136	5.47 ± 1.87	<0.001[b]
MELD[a]	688	1.37 ± 2.05; 0.91 (0-14.94)[g]	151	1.45 ± 3; 0 (0-19.9)[g]	0.23
APRI[a]	702	0.16 ± 0.24	157	0.3 ± 0.23	<0.001[b]

Continued

	HCV− (n = 707)		HCV+ (n = 160)		
Variable	No.	Mean ± SD or n (%)	No.	Mean ± SD or n (%)	p Value
Table 2 Continued					
APRI, by range[c]					
≤0.5	702	685 (97.6)	157	137 (87.3)	<0.001[b]
0.5–1.5		15 (2.1)		19 (12.1)	
≥1.5		2 (0.3)		1 (0.6)	
FIB4[a]	702	1.1 ± 1.2	157	1.8 ± 1.1	<0.001[b]
FIB4, by range[c]					
0–1	702	657 (93.6)	157	119 (75.8)	<0.001[b]
2–3		35 (5)		31 (19.7)	
≥4		10 (1.4)		7 (4.5)	

Abbreviations: ALT = alanine aminotransferase; APRI = aspartate transaminase to platelet ratio index; ART = antiretroviral therapy; AST = aspartate transaminase; FIB4 = fibrosis 4 score; HCV = hepatitis C virus; IADL = instrumental activities of daily living; JHU = Johns Hopkins University; MELD = Model for End-stage Liver Disease score; MSSM = Mt. Sinai School of Medicine; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; UCSD = University of California at San Diego; UTMB = University of Texas Medical Branch; WRAT = Wide Range Achievement Test.

[a] Mean ± SD; comparison using t test, unless otherwise noted.
[b] Significant.
[c] No. (%); comparison using Fisher exact test.
[d] IV drug use, composite: coded as yes if any of the IV drug use variables are yes.
[e] Based on item 20, "tiredness or fatigue," of Beck Depression Inventory, second edition.
[f] HCV RNA values were eliminated for 21 patients who are HCV− but HCV RNA detectable, $\log_{10}$ HCV RNA: serum >1.4473.
[g] Median (range); comparison using Wilcoxon rank-sum test.

was numerically higher in the HCV+ group, but only 10.8% of values were ≥3.25, the cutoff for defining significant fibrosis. The effect of current treatment for HCV is minimal. Forty-three of the entire cohort had a history of interferon treatment before entry in CHARTER, and 2 were on therapy at baseline and are in the confounded comorbidity category. No subjects were on direct-acting HCV drugs. Sensitivity analysis suggests these do not change outcomes.

HIV disease markers including current HIV treatment status, plasma viral load, and current CD4 were similar between HCV+ and HCV− groups (tables 1 and 2). This similar clinical status is also reflected by similar % IADL dependence with ~16% reporting dependence in activities of daily living.

Almost 40% (39.9%) of HCV-seronegative and 41.5% of HCV-seropositive patients in the incidental comorbidity group (p = 0.77) were neurocognitively impaired, as indicated by the clinical rating of global impairment. For the entire cohort comparison, 51.7% of HIV− patients were impaired while 52.6% of HCV+ patients were impaired (p = 0.8). No significant differences in GDS scores or in deficit scores among the 7 domains of neurocognitive functions were apparent between HCV+ and HCV− patients in the group as a whole or in the subgroup

without confounding conditions (tables 3 and 4, unadjusted). Trends in univariable analyses were toward better performance in the HCV+ group. Adjustment for liver injury did not change this conclusion. Among the 346 HCV-seropositive patients in whom plasma/serum HCV RNA concentration was measured, there was no relationship between HCV RNA and neurocognitive performance reflected by GDS (figure) or deficit scores within each cognitive domain (data not shown). Also, in the HCV-seropositive group there was no significant association between neurocognitive impairment and the FIB4 index.

DISCUSSION Observations that HCV replicates in the brain, inclusive of brain-specific evolution in HCV sequences[27] and immunohistochemical detection of virus in astroglia and macrophage-like brain cells, suggest that HCV might injure the brain.[28,29] Numerous reports have suggested neurocognitive effect of HCV infection, implying a potentially important role of this infection in disability.[7,8,10,11,16,18,19,30–32] Conversely, other studies have failed to find neurocognitive impairment linked to HCV antibody status or HCV RNA viral loads, particularly when careful attention to confounding sources of impairment are analyzed.[33–35]

Table 3 Neurocognitive performance association with HCV, for all subjects (n = 1,582), in unadjusted and adjusted analysis

Deficit score	Unadjusted model				Adjusted model (1)			
	Δ[a]	95% CI		p Value	Δ[a]	95% CI		p Value
GDS	−0.008	−0.07	0.055	0.81	−0.047	−0.105	0.01	0.11
Verbal DDS	−0.069	−0.144	0.006	0.07	−0.075	−0.15	0	0.05[b]
Executive functioning DDS	−0.043	−0.137	0.051	0.37	−0.033	−0.128	0.061	0.49
SIP DDS	−0.042	−0.114	0.03	0.25	−0.062	−0.136	0.011	0.098
learning DDS	−0.004	−0.092	0.084	0.93	−0.055	−0.14	0.03	0.21
Recall DDS	0.081	−0.005	0.168	0.065	0.013	−0.072	0.098	0.76
Work memory DDS	0.018	−0.069	0.105	0.68	−0.07	−0.156	0.017	0.11
Motor DDS	−0.063	−0.171	0.045	0.25	−0.095	−0.204	0.015	0.091
GDS	−0.017	−0.086	0.052	0.63	−0.003	−0.077	0.072	0.94
Verbal DDS	−0.036	−0.127	0.054	0.43	−0.032	−0.13	0.065	0.52
Executive functioning DDS	0.026	−0.087	0.14	0.65	0.04	−0.083	0.163	0.52
SIP DDS	−0.031	−0.119	0.058	0.5	−0.005	−0.1	0.089	0.91
Learning DDS	−0.047	−0.15	0.055	0.37	−0.031	−0.142	0.079	0.58
Recall DDS	0.019	−0.083	0.121	0.72	0.033	−0.077	0.143	0.55
Work memory DDS	−0.019	−0.123	0.085	0.72	−0.038	−0.15	0.074	0.51
Motor DDS	−0.024	−0.156	0.107	0.72	0.006	−0.136	0.148	0.94

Abbreviations: CI = confidence interval; DDS = domain deficit score; GDS = global deficit score; HCV = hepatitis C virus; SIP = speed of information processing.

Three adjusted models controlled for the following covariates: model 1: log10 HIV RNA—plasma, nadir CD4, Wide Range Achievement Test-oral reading score, education, ethnicity, comorbidity, and duration of HIV infection; model 2: covariates in model 1 and the 4 variables defining IV drug use (see table 1); model 3: covariates in model 2 and all the liver function markers: aspartate aminotransferase, alanine aminotransferase, Model for End-stage Liver Disease, aspartate transaminase to platelet ratio index, and fibrosis 4 index.

[a] Δ = Difference in the corresponding deficit score between HCV+ and HCV−.

[b] Significant.

The CHARTER study provides an opportunity to closely examine the effect of HCV coinfection on neurocognitive function in HIV-infected individuals. CHARTER was designed to collect a well-validated neurocognitive assessment including most domains of function that have proved sensitive for HAND. Our results show that neurocognitive function is similar in HIV-infected patients who are and are not coinfected with HCV. Inclusion of >400 HCV-infected patients with twice that number of controls, all with careful assessment of HIV status and neurocognitive evaluation, makes it unlikely that clinically significant cognitive impairment was missed in our cohort. The lack of association between impairment and serum HCV RNA concentration further supports the probability that, at least in absence of advanced liver disease, HCV does not contribute to neurocognitive impairment in HIV-infected individuals. This does not refute the role of clinical or subclinical hepatic encephalopathy caused by advancing liver disease or the effect of HCV therapy, especially interferon, in causing neurologic symptoms.[36] It is noteworthy that close to 60% of our population had detectable plasma

HIV RNA, and it is unclear whether an effect of HCV infection would have emerged if patients with better control of HIV were studied. However, sensitivity analysis taking into account detectable plasma HIV RNA or prior AIDS diagnosis failed to show significant relationships between HCV serostatus and neurocognitive function. Like other comparisons, our HCV+ cohort was older, less educated, more exposed to IV drugs, and from minority demographic populations, all findings unlikely to be advantageous to NP performance. Performing a more complete NP battery with good normative data may help explain the absence of impairment we demonstrate in comparison to some prior studies. It is interesting that where trends occurred, they favored better performance for the HCV+ group, leaving little doubt that we see no significant HCV+-driven effect in this population (table 3). Other associations remain to be explored, including systematic differences in antiviral therapy or differences in CNS inflammation. At present, we do not have any hypothesis explaining neuroprotection in the HCV cohort that might obscure a deleterious HCV+ effect.

| Table 4 | Neurocognitive performance association with HCV, for only those individuals with minimal comorbidities (n = 867), in unadjusted and adjusted analysis |

Deficit score	Unadjusted model				Adjusted model (1)			
	Δ[a]	95% CI		p Value	Δ[a]	95% CI		p Value
GDS	0.01	−0.061	0.082	0.78	0.023	−0.05	0.097	0.54
Verbal DDS	−0.036	−0.128	0.056	0.44	−0.004	−0.099	0.092	0.94
Executive functioning DDS	0.026	−0.094	0.146	0.67	0.07	−0.056	0.196	0.28
SIP DDS	0.015	−0.068	0.097	0.73	0.029	−0.058	0.117	0.51
Learning DDS	−0.032	−0.148	0.083	0.58	−0.024	−0.143	0.096	0.7
Recall DDS	0.064	−0.047	0.175	0.26	0.054	−0.062	0.169	0.36
Work memory DDS	0.027	−0.081	0.136	0.62	−0.007	−0.121	0.107	0.91
Motor DDS	−0.004	−0.131	0.122	0.95	0.048	−0.087	0.183	0.49
GDS	0.062	−0.024	0.148	0.16	0.076	−0.019	0.171	0.12
Verbal DDS	0.05	−0.062	0.162	0.38	0.029	−0.096	0.153	0.65
Executive functioning DDS	0.136	−0.012	0.284	0.073	0.137	−0.027	0.301	0.1
SIP DDS	0.064	−0.039	0.167	0.22	0.074	−0.038	0.185	0.2
Learning DDS	0	−0.14	0.141	1	0.036	−0.119	0.192	0.65
Recall DDS	0.092	−0.044	0.229	0.18	0.102	−0.048	0.252	0.18
Work memory DDS	0.053	−0.081	0.187	0.44	0.076	−0.072	0.224	0.32
Motor DDS	0.064	−0.095	0.224	0.43	0.093	−0.082	0.267	0.3

Abbreviations: CI = confidence interval; DDS = domain deficit score; GDS = global deficit score; HCV = hepatitis C virus; SIP = speed of information processing.

Three adjusted models controlled for the following covariates: model 1: log10 HIV RNA—plasma, nadir CD4, Wide Range Achievement Test–oral reading score, education, ethnicity, comorbidity, and duration of HIV infection; model 2: covariates in model 1 and the 4 variables defining IV drug use (see table 2); model 3: covariates in model 2 and all the liver function markers: aspartate aminotransferase, alanine aminotransferase, Model for End-stage Liver Disease, aspartate transaminase to platelet ratio index, and fibrosis 4 index.

[a] Δ = Difference in the corresponding deficit score between HCV+ and HCV−.

A prior published analysis of MRI findings of CHARTER patients showed in a subset that HCV was associated with a larger volume of abnormal white matter.[37] While this would be consistent with HCV-associated brain injury, it remains an associative finding that may relate to some of the other differences in the populations. Imaging changes do not necessarily have functional significance and in any case the imaged group was a subset, and may not have fully represented this population. Further detailed imaging analysis is planned.

Our participants are intended to be a representative sample of HIV+ patients followed in academic treatment centers in the United States. As such, they are recognized to have numerous other conditions that might affect their cognitive performance status. In classifying these, HCV was considered one condition that might contribute. However, given the uncertainty concerning its effect, it was not considered sufficient to exclude a patient from the incidental or lowest comorbidity class. Thus, we have a substantial sample of HCV-positive subjects compared with other patients with minimal confounding conditions. This analysis would not be confounded by excessive

noise from other causes of cognitive impairment that might obscure small differences between monoinfected and coinfected groups. However, we also performed the comparison for the entire population so no studied patients were excluded. If HCV effects depend on interaction with other potential brain conditions to manifest impairment, this large comparison should demonstrate the difference. In neither grouping of patients can we demonstrate a significant effect of HCV infection on carefully measured cognitive performance.

Our study has a number of limitations. Since all of our subjects were HIV coinfected, we cannot test the neurocognitive effect of HCV infection alone. Since HIV may cause significant cognitive impairment, it is possible this could obscure less evident HCV-induced impairment. This possibility seems unlikely, especially in light of prior reports that suggested additive deleterious cognitive effects of HCV in HIV-infected patients.[11,15] While our study includes HIV-treated and HIV-untreated patients, interactions of HIV disease status and treatment with the manifestations of HCV infection are not isolated in our study, but multivariable analyses of

Figure Neurocognitive performance is not associated with hepatitis C virus viral load
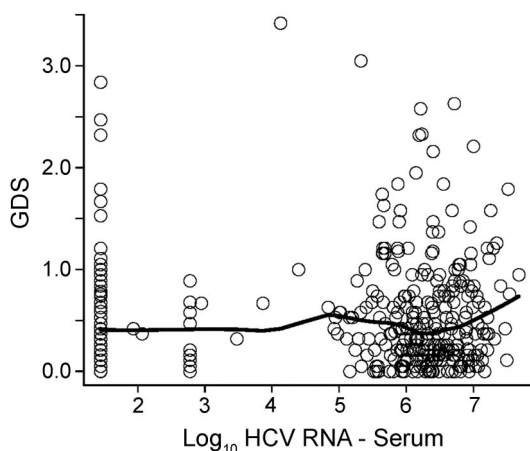
The association between neurocognitive performance vs log10 hepatitis C virus (HCV) RNA in serum for the HCV+ cohort (n = 346). The smooth curve through the data in the plot was computed using Lowess method. Linear regression was used for this analysis and no correlation was found between global deficit score (GDS) and log10 HCV RNA in serum (β = −0.002, 95% confidence interval [−0.032, 0.028], p = 0.90).

neurocognitive outcomes adjusted for HIV RNA and other potential HIV-associated clinical variables failed to show significant or consistent effects, making it unlikely that HIV viral status contributes to these negative findings.

Current progress in HCV therapeutics promises to make cure of HCV infection much more practical.[20] The risks associated with chronic HCV infection including liver failure and hepatocellular cancer are sufficient justifications for treating this coinfection. However, our results suggest that the neurocognitive dysfunction currently observed in our HIV population cannot rightfully be attributed to HCV coinfection. Other mechanisms must be investigated in order to design more effective therapy for the persisting HIV-associated neurocognitive impairment.

AUTHOR CONTRIBUTIONS

Dr. Clifford is the primary author on this manuscript and as such he was responsible for study conceptualization and design. All study data were available to him and he planned the statistical analyses and performed the interpretation of the results. Dr. Clifford thereby assumes responsibility for the accuracy of the data, analysis, and interpretation. Dr. Vaida is the CHARTER statistician and led the statistical analysis. He contributed to this manuscript by assisting with study design, data analysis, drafting and revision of the manuscript. Y.-T. Kao provided data management and statistical analysis, and assisted in study design, data analysis, interpretation of data, drafting and revision of the manuscript. D.R. Franklin is CHARTER center manager and he provides integral coordination and dissemination of CHARTER data. He contributed to this manuscript by assisting with study design, data analysis, drafting and revision of the manuscript. Dr. Letendre made considerable contributions through management and coordination of the laboratory data, and assisted with study design, analysis, and interpretation, as well as revisions to the manuscript.

Dr. Collier assisted with primary data collection, drafting, and revising the manuscript. Dr. Marra assisted with primary data collection, drafting, and revising the manuscript. Dr. Gelman assisted with primary data collection, drafting, and revising the manuscript. Dr. McArthur assisted with primary data collection, drafting, and revising the manuscript. Dr. Morgello assisted with primary data collection, drafting, and revising the manuscript. Dr. Simpson assisted with primary data collection, drafting, and revising the manuscript. Dr. Grant assisted with study design, data interpretation, drafting and revising the manuscript. Dr. Heaton assisted with study design, data interpretation, drafting and revising the manuscript.

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