Effects of active HCV replication on neurologic status in HIV RNA virally suppressed patients

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ABSTRACT

Background: Hepatitis C virus (HCV) is a frequent copathogen with HIV. Both viruses appear to replicate in the brain and both are implicated in neurocognitive and peripheral neuropathy syndromes. Interaction of the viruses is likely to be complicated and better understanding of the contributions of each virus will be necessary to make evidence-based therapeutic decisions.

Methods: This study was designed to determine if active HCV infection, identified by quantitative HCV RNA determination, is associated with increased neurocognitive deficits or excess development of distal sensory peripheral neuropathy in HIV coinfecting patients with stable HIV viral suppression. The AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT) study was the source of subjects with known HIV treatment status, neurocognitive and neuropathy evaluations, and HCV status. Subjects were selected based on HCV antibody status (249 positive; 310 negative).

Results: HCV RNA viral loads were detectable in 172 participants with controlled HIV infection and available neurologic evaluations in the ALLRT. These participants were compared with 345 participants with undetectable HCV viral load and the same inclusion criteria from the same cohort. Neurocognitive performance measured by Trail-Making A or B and digit symbol testing was not dissimilar between the 2 groups. In addition, there was no significant association between active HCV replication and distal sensory neuropathy.

Conclusion: Clinically significant neurocognitive dysfunction and peripheral neuropathy were not exacerbated by active hepatitis C virus infection in the setting of optimally treated HIV infection.

Neurology® 2009;73:309–314

GLOSSARY

ALLRT = AIDS Clinical Trials Group Longitudinal Linked Randomized Trials; **CI** = confidence interval; **HAART** = highly active antiretroviral therapy; **HCV** = hepatitis C virus; **IDU** = injection drug use; **VL** = viral load; **WAIS-R** = Wechsler Adult Intelligence Scale-Revised.

Hepatitis C virus (HCV) is a disease of over 200 million people worldwide.^{1,2} It is common in the HIV-infected population, where it is estimated that 25%–40% of individuals are coinfecting with HCV in the United States, with a higher proportion of the injection drug using (IDU) population coinfecting. In the era of highly active antiretroviral therapy (HAART), careful evaluation of clinic populations that have access to HIV therapy reveals that many persons remain cognitively impaired.³ One possible contributor to impairment is untreated HCV infection. HCV is believed to replicate in the brain and CSF compartments.^{4–7} There are reports suggesting that HCV is a cause of cognitive impairment.^{8–13} HCV-associated neurologic impairment might explain ongoing impairment found in HIV-treated coinfecting patients, implying the importance of future therapeutic efforts for HCV.

One of the difficulties in the analysis of HCV–HIV coinfection is that often the infected and uninfected participants display notable differences with respect to potential confounders, including

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Supported by NIH grants including Neurologic AIDS Research Consortium Grant NS32228 from NINDS and AIDS Clinical Trials Grant AI068636 from NIAID.

Disclosure: Author disclosures are provided at the end of the article.

history of IDU, sex, and educational status. While studies have sought to adjust for the divergence of risk factors in these groups during analyses, this has routinely been difficult to achieve and is optimally addressed in study design.¹⁴

The AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT) study provides an opportunity to examine the effect of active HCV replication on neuropsychological function and neuropathy in HIV-infected individuals. Our analyses investigate whether active HCV infection (HCV viremia) is associated with either neurocognitive impairment or peripheral neuropathy.

METHODS Participants were selected from ALLRT, a cohort consisting of participants prospectively enrolled into randomized treatment clinical trials of the ACTG who have agreed to be followed long-term for the purpose of evaluating clinical, virologic, immunologic, neurologic, and pharmacologic outcomes associated with long-term treatment of HIV with potent antiretroviral therapies. Participants provide written informed consent. Each ACTG study site received approval from their designated institutional review board prior to protocol initiation. These participants had brief neurocognitive quantitative examinations and a brief peripheral neuropathy evaluation. HCV antibody status was determined as part of ALLRT.

Selection of samples to study. We selected all HCV antibody-positive participants in ALLRT with a plasma sample available at least 20 weeks post randomization on an ACTG HIV treatment trial and who were HIV virally suppressed (defined as having at least 2 subsequent and consecutive HIV plasma viral load (VL) measurements of less than 400 copies/mL in a 6-month period). If there were more than 2 HIV RNA measurements reported in a 6-month period, they all had to be less than 400 copies/mL. We selected the plasma sample based on the draw date closest to the neurologic examination; the majority (92%) of plasma samples were collected on the same day as the neurologic evaluation. Additional criteria required for inclusion in the dataset included a neurologic examination following the HCV antibody test result (at least 20 weeks post-randomization), available plasma sample, and 6 months of HIV virologic suppression prior to (and including) the neuropsychological examination. HCV antibody-negative participants eligible for inclusion in the analysis were selected using the same criteria. Final subjects were selected randomly from this group. However, in an effort to balance the 2 groups, especially on the important difference of IDU, all HCV-negative IDU subjects were selected. A 6-level distribution of education level and race among the 249 HCV antibody-positive subjects was determined and the HCV-negative population was selected so as to have a corresponding distribution. After 248 HCV-negative samples were selected at random, the remaining HCV-negative injection drug users ($n = 22$) who qualified for the study were added to the group for a total of 310 HCV-negative samples.

Hepatitis C determination. The HCV Taqman quantitative VL assay (Roche Molecular Systems, Branchburg, NJ) with a lower limit of detection of 40 IU/mL was performed on all samples to determine HCV disease activity. The test was performed

in a CAP- and CLIA-certified laboratory at Washington University in St. Louis. Validation of the technique was performed in this laboratory prior to testing. HCV antibody-positive samples were run alone, while the antibody-negative samples were batched with 3 specimens per assay, making the theoretical limit of detection 120 IU/mL for HCV antibody-negative determinations. However, the lowest VL recorded among the HCV antibody-negative group with detectable VL was $>700,000$ IU/mL.

Neurologic evaluations. The neurologic assessment included the Trailmaking A and B tests¹⁵ and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) digit symbol test.¹⁶ These tests provide quantitative assessment in the areas of motor persistence, sustained attention, response speed, visuomotor coordination, and conceptual shifting and tracking. The raw scores were standardized (by age, education, gender, and race) into Z scores, and then a composite neuropsychological (NPZ3) score was constructed as the average of the standardized scores. Norms for development of Z scores were performed by Dr. Michael Taylor using published norms¹⁷ (WAIS III—WMS-II—WIAT-II Scoring Assistant [computer software]; The Psychological Corporation, San Antonio, TX). Trained and certified site personnel conducted a brief peripheral neuropathy examination that evaluated distal vibratory sensation, distal reflexes, and symptoms of peripheral neuropathy. Neuropathy was defined by presence of at least mild loss of vibration sensation in both great toes bilaterally or ankle reflexes absent or hypoactive relative to knees bilaterally, based on examination by a trained individual at the site. When these findings were combined with subjective peripheral neuropathy grade greater than 0, indicating some subjective change in distal sensation, neuropathy was scored as symptomatic neuropathy.

Data collection. Other factors examined in analysis include demographic information (age, race, sex) and self-reported IDU, which were collected at baseline, when subjects entered their clinical trial. HIV-1 RNA VL and CD4⁺ T-cell counts were collected at baseline and every 16 weeks while on study; antiretroviral use was updated every 16 weeks. Total years of education were collected the first time the neuropsychological battery is administered. Plasma samples were collected every 16 weeks, frozen at -70°C , shipped, and stored at a central laboratory.

Statistical methods. Univariate analyses were used to describe the relationship between covariates and HCV VL status; HCV VL status was defined as positive (HCV VL >40 IU/mL) or negative (HCV VL ≤ 40 IU/mL). Exact tests were used to compare nominal variables (sex, race, IDU, d-drug use) and Kruskal-Wallis tests were used with continuous variables (age, years of education, CD4, log[HCV RNA]). (d-Drugs are the neurotoxic nucleosides including d4T [stavudine], ddI [didanosine], and ddC [zalcitabine].) Univariate models describe the mean and SD of the individual and NPZ3 test scores among the HCV VL and HCV antibody groups. Linear models were used to estimate the effect size and 95% confidence intervals (CI) of positive HCV VL and HCV antibody-positive groups on each of the individual neurocognitive tests, as well as the NPZ3 score, while controlling for IDU, education, sex, race, and age. Logistic regression was used to estimate the association of HCV VL positivity with neuropathy and symptomatic neuropathy while controlling for covariates. A scatterplot displays the relationship between cognitive function (as measured by NPZ3) and log(HCV RNA) for HCV VL positive participants. There is no adjustment for multiple testing.

RESULTS Among 3,413 participants enrolled in ALLRT, 3,147 (92%) had an HCV antibody titer

Table 1 Demographics and potential confounders by HCV VL status

	HCV VL status		p Value
	≤40 IU/mL (n = 345)	>40 IU/mL (n = 172)	
Age, y	41 (34, 47)	45 (40, 49)	<0.01*
Education, y	13 (12, 16)	12 (11, 14)	<0.01*
Male	276 (80)	141 (82)	0.64†
White	152 (44)	55 (32)	0.01†
Black	118 (34)	80 (47)	
Other	75 (22)	37 (22)	
IV drug use	87 (25)	91 (53)	<0.01†
CD4, cells/mm ³	452 (313, 649)	455 (296, 640)	0.58*
d-Drug use	96 (28)	43 (25)	0.53†
Log ₁₀ (HCV RNA)		6.05 (5.51, 6.38)	N/A

Data are median (Q1, Q3) or n (%). d-Drugs are the neurotoxic nucleosides including d4T (stavudine), ddI (didanosine), and ddC (zalcitabine).

*Kruskal-Wallis test.

†Exact test.

HCV = hepatitis C virus; VL = viral load.

test result in the database; 373 (12%) participants were HCV antibody-positive and 2,773 (88%) were HCV antibody-negative (there was one indeterminate test result). Of the 373 participants with positive HCV antibody test results, 249 (67%) fulfilled the additional criteria to be included in the analysis. There were 310 antibody-negative subjects selected for inclusion. A total of 42 samples were unavailable for testing (21 from each group); 517 samples were tested for HCV VL. Of the 289 HCV antibody-negative samples tested, 5 had detectable HCV VLs. Of the 228 antibody-positive subjects tested, 61 had negative HCV VLs. The primary comparison was conducted between the 172 participants with detectable HCV VLs (HCV VL positive with >40 IU) and the 345 with undetectable HCV VL (HCV VL negative).

The HCV VL+ participants were slightly older than HCV VL−, with a median age of 45 years compared to 41 in the HCV− participants ($p < 0.01$) (table 1). Although there was a statistical difference ($p < 0.01$) in educational status, the 1-year differ-

ence in median years of education was not substantial. The patient population was approximately 80% men, without a significant difference in the groups, but race and IDU were imbalanced, with the HCV VL+ participants being more likely to be black or to have a history of IDU. Despite the inclusion of all HCV antibody-negative participants with a history of IDU, there were still a larger percentage of IDU among the HCV VL+ subjects (53% HCV VL+ vs 25% HCV VL−). HIV disease status was well matched, with baseline CD4 counts of approximately 450 cells/mm³ and prior d-drug use of approximately 25% in each group. Median log HCV VL among the positive group was 6.05 IU/mL.

The results of neurologic testing comparing HIV-positive patients with positive or negative HCV VL status are shown in table 2. The primary measure of the NPZ3 showed both samples performing slightly below norms with mean scores of −0.46 for the HCV VL− participants and −0.59 for the HCV VL+ participants in univariate analyses. The mean effect of HCV VL >40 was −0.11 (95% CI [−0.27, 0.04], p value = 0.14) in an adjusted model. There were no significant differences observed for the individual tests. CIs suggested that the effects HCV >40 could be as large as 0.33. An evaluation of the effect of the magnitude of HCV VL on cognitive function did not reveal an observable correlation (figure).

Forty-two percent of the HCV VL-positive participants had neuropathy while 36% of the HCV VL-negative group had neuropathy on examination. Symptomatic neuropathy was found in 19% HCV VL+ and 12% HCV VL− (table 3). The association between HCV VL status and neuropathy is not significant, although odds ratios as large as 1.38 (neuropathy) or 2.08 (symptomatic neuropathy) are still consistent with these data.

Additional exploratory analyses considered the same comparisons regarding neurocognitive performance and neuropathy status based on HCV antibody status without consideration of HCV VL. The potential HCV affected group is larger when anti-

Table 2 Neuropsychological function by HCV VL status

Test	Univariate HCV VL status	Adjusted*		
	>40 IU/mL, mean (SD)	≤40 IU/mL, mean (SD)	Effect of HCV >40 (95% CI)	p Value
NPZ3	N = 170; −0.59 (0.76)	N = 336; −0.46 (0.83)	−0.11 (−0.27, 0.04)	0.14
Trailmaking A	N = 172; −0.38 (1.07)	N = 344; −0.23 (1.17)	−0.06 (−0.28, 0.15)	0.56
Trailmaking B	N = 171; −0.12 (1.09)	N = 338; −0.02 (1.18)	−0.11 (−0.33, 0.11)	0.31
Digit Symbol	N = 171; −1.25 (0.70)	N = 343; −1.15 (0.78)	−0.13 (−0.27, 0.01)	0.07

*Adjusted for injection drug use, education, sex, race, and age in a linear regression model.

HCV = hepatitis C virus; VL = viral load; CI = confidence interval.

Figure Scatterplot of NPZ3 score by log(HCV RNA VL) for participants with hepatitis C viral load >40 IU/mL

body alone is considered, yielding 249 HCV antibody-positive and 310 HCV antibody-negative participants for comparison. In this analysis, adjusted for IDU, education, sex, race, and age, the NPZ3 for HCV antibody-negative participants was -0.41 while for antibody positives it was -0.62 (95% CI $[-0.31, -0.03]$, $p = 0.02$), a result driven by both Trailmaking B and Digit Symbol test results (table 4). Similarly, the presence of neuropathy or symptomatic neuropathy was compared in the HCV antibody-positive vs negative groups. While the overall presence of neuropathy was not significantly associated with HCV antibody status, symptomatic neuropathy was more common in the HCV antibody-positive group (OR = 3.81, 95% CI $[1.06, 13.73]$, $p = 0.04$).

DISCUSSION These analyses suggest that neither neurocognitive disability nor neuropathy in HCV/

HIV coinfection is significantly driven by active replication of HCV in the plasma. This study is important as it includes a relatively large sample size and utilizes HCV VLs to define active HCV disease. This result suggests that clinically important neurologic deficits are unlikely to be the result of HCV viral replication.

It is interesting that when HCV antibody status is considered, a marginally significant difference in performance favoring the HCV antibody-negative group emerges, much as we saw in our previous antibody-based retrospective analysis of participants in a single ACTG treatment trial.¹⁴ This might suggest that a history of infection by HCV reflected in the antibody status is more important than the contribution of HCV replication when the performance is measured. While this could be the result of prior neurologic damage, it might also be biased more heavily by group differences that might impact performance, most notably for IDU, education, or race.

This analysis has several limitations. It is a retrospective study and we were unable to completely match on the confounders believed to be important. Instead we attempted to statistically adjust our analyses to minimize the bias these confounders might introduce. There may be additional unrecognized/unmeasured confounders for which we could not control. Potential confounders not analyzed included alcohol use, diet, liver function status, and CSF (HCV and HIV) VL status. Had we found a significant decrement in performance in the active HCV population, these uncontrolled confounders might be of greater concern. However, it seems unlikely that they would be protective and result in a false negative finding in our study.

The measures that we used were also brief and administered by staff that was not specialty trained in neurology. More rigorous or more difficult tests might detect functional changes in other domains, or smaller degrees of dysfunction. However, these are not practical in exploratory studies of large cohorts such as the ALLRT study, and brief and robust measures such as our battery have served well to probe neurocognitive function. The performance characteristics of this brief neurocognitive and peripheral neuropathy battery have been characterized and validated with this group.¹⁸

One important way in which this study differs from others that have attempted to describe the specific impact of HCV in the setting of HIV infection is that we have chosen to control the impact of the HIV infection by studying HCV in the setting of virologically controlled HIV infection. It might be true that an entirely different dynamic could occur if both infections were untreated (i.e., with higher HIV-1 RNA VLs) or unsuc-

Table 3 Neuropathy or symptomatic neuropathy by HCV VL status

HCV VL status	Neuropathy/symptomatic neuropathy		
	Yes	No	
>40 IU/mL	67/30	92/129	159
≤40 IU/mL	115/39	200/276	315
Total	182/69	292/405	474

Adjusted for injection drug use, education, d-drug use, sex, race, and age. d-Drugs are the neurotoxic nucleosides including d4T (stavudine), ddl (didanosine), and ddC (zalcitabine). Neuropathy: odds ratio = 0.88, 95% CI (0.57, 1.38), p value = 0.59; symptomatic neuropathy: odds ratio = 1.16, 95% CI (0.65, 2.08), p value = 0.62. HCV = hepatitis C virus; VL = viral load.

Table 4 Neuropsychological function by HCV antibody (Ab) status

Test	Univariate HCV Ab status	Adjusted*		
	HCV Ab+, mean (SD)	HCV Ab−, mean (SD)	Effect of HCV >40 (95% CI)	p Value
NPZ3	N = 246; −0.62 (0.78)	N = 302; −0.41 (0.85)	−0.17 (−0.31, −0.03)	0.02
Trailmaking A	N = 219; −0.42 (1.11)	N = 309; −0.19 (1.19)	−0.14 (−0.34, 0.06)	0.16
Trailmaking B	N = 247; −0.19 (1.13)	N = 304; 0.03 (1.19)	−0.20 (−0.40, 0.00)	0.05
Digit Symbol	N = 248; −1.25 (0.76)	N = 308; −1.11 (0.78)	−0.13 (−0.25, 0.00)	0.05

*Adjusted for injection drug use, education, sex, race, and age in a linear regression model.

HCV = hepatitis C virus; CI = confidence interval.

cessfully treated. However, we believe that in a practical sense, the major issue about coinfection will revolve around the additional impact of HCV for the majority of HIV-positive patients who currently benefit from successful control of their HIV, but are concerned about the additional risk to the nervous system of a second potentially neuroinvasive virus. We believe the observations that we report are relevant to this population and suggest that neurologic consequences will not be the driving feature requiring HCV treatment.

Our findings are largely consistent with those from the coinfection experience reported from the Manhattan HIV Brain Bank study.¹⁹ Similarly, others²⁰ did not find that HCV/HIV coinfection resulted in greater neuropsychological impairment than HCV alone. A rather large study in the Hemophilia Growth and Development Study reported that after controlling for multiple factors, HCV mono-infection was not associated with deficits in adaptive behavior, intelligence, or attention/concentration.²¹ Still, several investigators have carefully studied substantial numbers of patients and concluded that HCV is associated with negative neurocognitive consequences. Letendre et al.²² concluded that HCV contributed to neuropsychological deficits observed in a study of HIV-infected and stimulant-dependent participants. More detailed neuropsychometric analysis was performed as part of this study, but the numbers of HCV antibody-positive subjects (83) were smaller than our study, and the demographic characteristics between populations diverged significantly in this study.

Our observations are consistent with observations in a study of HAART, HIV, and HCV coinfection in which untreated coinfecting patients showed worse performance on testing than HIV mono-infected patients, but after 6 months of HIV therapy, the groups no longer differed.²³ While the observations in this study were interpreted to suggest interaction of active coinfection, they also replicate our observation that in treated HIV-positive patients, coinfecting participants perform similarly to the mono-infected popula-

tion, suggesting that HAART may eliminate negative impact of coinfection.

Our analysis is one of the largest to link HCV VL data with specific quantitative neurologic testing. In undertaking the project we could not get reliable data on the degree of incongruity to be expected between HCV antibody testing and demonstration of HCV VL. The evaluation of the HCV antibody-negative subjects yielded 5 in whom HCV VLs ranged from 741,000 to 4,800,960 IU/mL. Because the testing of antibody and RNA was not performed precisely at the same time, it could be that the incongruent results were due to recent conversions, rather than false negative results. However, others have described as many as 19% false negative HCV antibody testing in the setting of HIV infection.²⁴

Our study makes an important statement about pragmatic issues in the setting of HIV and HCV coinfection. While both viruses likely enter and can replicate in the brains of patients, and may well impact neurocognitive function as a result of this, when the HIV infection is pharmacologically controlled, the addition of HCV appears not to have clinically important additive impact. The long-term consequences of HCV coinfection remain important, and will be necessarily a focus for ongoing treatment development due to the significant morbidity and mortality of liver disease in this population. The liver disease will independently impair brain function. However, it appears that primary neurocognitive disease is unlikely to represent a critical reason for initiation of HCV therapy in the setting of coinfection, and it is unlikely to be a major cause of neurocognitive impairment that is still seen in the treated HIV populations.

ACKNOWLEDGMENT

The authors thank the patients volunteering for the ALLRT study, and the contributing AIDS Clinical Trials Units, their investigators, and staffs, who collected the samples and clinical data used for this analysis.

DISCLOSURE

Dr. Clifford serves on scientific advisory boards or consults for Biogen Idec, Elan Pharmaceuticals, Roche Pharmaceuticals, Forest Labs, Genen-

tech, GlaxoSmithKline, Millennium Consulting, Schering Plough, Bristol Myers Squibb, and Genzyme; received research support from Pfizer, Schering Plough, Bavarian Nordic, GlaxoSmithKline, Tibotec, Boehringer Ingelheim, Gilead, and Biogen; and receives research support from the NIH #UO1 NS32228 (PI), #UO1 AI69495 (PI), NIMH 22005 CHARTER Project (Site PI), NIDA #RO3 DA022137 (Investigator), NIMH #MH058076 (Site PI), #R21 3857-53187 (Fogarty Institute, PI). Dr. Smurzynski reports no disclosures. Ms. Park reports no disclosures. Mr. Yeh reports no disclosures. Dr. Zhao reports no disclosures. Ms. Blair reports no disclosures. Dr. Arens serves as an Associate Editor for the *Journal of Clinical Virology*. Dr. Evans serves on scientific advisory boards for Genentech and the HIV Neurobehavioral Research Center; serves as Guest Editor for the *Drug Information Journal*, Associate Editor for *Case Studies in Business, Industry, and Government*, and Academic Editor for *PLoS Clinical Trials*; receives honoraria membership on Data Safety and Monitoring Boards for the NIH, Genentech, Pfizer, the Harvard Clinical Research Institute, and Massachusetts General Hospital; receives honoraria for teaching short-courses at the American Statistical Association and the American Neurological Association; serves as a consultant for CIS Biotech; serves on an FDA advisory committee; and receives research support from the NIH (Statistical Center).

Received February 9, 2009. Accepted in final form April 21, 2009.

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