Title

Neurocognitive impairment is worse in HIV/HCV-coinfected individuals with liver dysfunction

Journal

Journal of NeuroVirology, 25(6)

ISSN

1355-0284

Authors

Barokar, Jyoti
McCutchan, Allen
Deutsch, Reena
et al.

Publication Date

2019-12-01

DOI

10.1007/s13365-019-00767-6

Peer reviewed

HHS Public Access

Author manuscript

J Neurovirol. Author manuscript; available in PMC 2020 December 01.

Published in final edited form as:

J Neurovirol. 2019 December ; 25(6): 792–799. doi:10.1007/s13365-019-00767-6.

Neurocognitive Impairment is Worse in HIV/HCV Co-Infected Individuals with Liver Dysfunction

Jyoti Barokar[1], **Allen McCutchan**[2], **Reena Deutsch**[1], **Bin Tang**[1], **Mariana Cherner**[1], **Ajay R. Bharti**[2]

[1]Department of Psychiatry, University of California, San Diego, USA

[2]Department of Medicine, University of California, San Diego, USA

Abstract

Infections with HIV and Hepatitis C Virus (HCV) can individually and jointly contribute to neurocognitive impairment (NCI). Rates of NCI in HIV/HCV co-infected persons range from 40% to 63% but its correlates have not been described. In this study, we examined HIV/HCV co-infected adults on antiretroviral therapy (ART) with undetectable HIV RNA in blood (n = 412) who were assessed using a comprehensive neuropsychological test battery. Demographics, host and viral biomarkers, and markers of liver dysfunction were compared between impaired (n = 198) and unimpaired (n = 214) participants using logistic regression. The cohort was predominantly middle-aged men, half of whom (48%) had NCI. The odds of NCI increased by almost two-fold when serum albumin was <4 g/dL, 1.7-fold when alanine aminotransferase (ALT) levels were >50 IU/L, and 2.2-fold with every unit increase in $\log_{10}$ AST to Platelet Ratio Index (APRI). These readily available clinical biomarkers of NCI measure hepatic injury and/or dysfunction, suggesting a mechanism for the effects of HCV infection on NCI. They may identify patients at increased risk of NCI who could be prioritized for early initiation of HCV treatment to protect or improve cognition.

Summary

Readily available clinical biomarkers such as serum albumin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) may help identify patients at increased risk of neurocognitive impairment for interventions to protect or improve cognition.

Corresponding Author: Ajay R. Bharti, MD, Division of Infectious Diseases, Department of Medicine, University of California, San Diego, CA 92093. abharti@ucsd.edu; Tel: (619) 543-8091; Fax (619) 543-0938. Alternate Corresponding Author: Allen McCutchan, MD, Division of Infectious Diseases, Department of Medicine, University of California, San Diego, CA 92093. amccutchan@ucsd.edu; Tel: (619) 543-5052; Fax (619) 543-0938.

Conflict of Interest

The authors disclose no conflict of interest related to the manuscript.

Keywords

HIV/HCV co-infection; neurocognitive impairment; APRI; hepatic inflammation; liver fibrosis

INTRODUCTION

HIV and HCV are independently associated with neurocognitive impairment (NCI) and about half of dually-infected persons are cognitively impaired. NCI in HIV mono-infected persons persists despite suppressive antiretroviral therapy (ART)[1] and can adversely affect activities of daily living (ADL), driving, and morbidity.[2] Among those with HIV/HCV co-infection, identifying factors associated with NCI could help select those at an increased risk. Prioritizing such patients for neuropsychological assessment and HCV treatment with the newer direct acting antivirals (DAAs) may protect or improve their brain function. However, correlates of NCI in HIV/HCV co-infected patients have not been identified.

HCV treatment may reverse its effect on the brain, but studies that have tested this hypothesis found no improvement after interferon and ribavirin therapy.[3,4] This is possibly because interferon (IFN) itself contributes to cognitive dysfunction.[4] The new DAAs allow for IFN-free regimens and have been shown to reverse the effects of HCV on brain magnetic resonance spectroscopy (MRS) measures of neuronal integrity.[5] Whether this reversal correlates with improvement in cognition has not been well studied. A small, uncontrolled study observed improvement in cognitive function in several domains after treatment with DDAs, but did not account for practice effects from repeated testing.[6]

This study investigated the correlates of NCI among HIV/HCV co-infected persons on suppressive ART.

METHODS

Participants

HIV/HCV co-infected participants (n = 412) were selected from those enrolled in several National Institute of Health (NIH)-funded studies at the HIV Neurobehavioral Research Program (HNRP) of the University of California, San Diego (UCSD). Written informed consent was obtained at enrollment in the original studies and the UCSD IRB approved this retrospective analysis. Inclusion criteria were: (1) age ≥18 years, (2) HIV infection with HIV RNA <50 copies/mL at the time of NP testing, and 3) HCV coinfection based on one or more of the following: HCV antibody, HCV RNA in blood or self-report, (4) complete neuropsychological (NP) assessment. Exclusion criteria included conditions that could result in irreversible brain injury such as CNS opportunistic infections, head trauma or cerebrovascular disease, and other conditions known to cause cognitive impairment such as hypothyroidism. We did not exclude those with history with seizures and depression. In univariable analysis, history of seizures was not associated with NCI. For eligible participants with multiple NP assessments, only the initial NP test data were included.

Neurocognitive function assessment

All participants underwent assessment using a standardized, comprehensive NP test battery that assesses seven cognitive domains affected by HIV: learning, recall, attention/working memory, speed of information processing, verbal fluency, executive functioning, and motor skills.[7] Test scores were standardized using published normative data that adjusts for age, gender, education, race, and ethnicity. These were combined to create seven domain-specific deficit scores (DDS) and a global deficit score (GDS) that reflects the number and severity of below-expected performance on individual tests. The GDS ranges from 0 (normal) to 5 (severely impaired) with impairment defined as GDS ≥ 0.5, a well validated definition.[7]

Laboratory assays

Blood samples collected and stored at −80° C at the same visit as NP testing were analyzed. HCV RNA was quantified in plasma by reverse transcription polymerase chain reaction (RT-PCR) (Roche COBAS AmpliPrep/COBAS TaqMan). Routine clinical and chemistry panels (electrolytes, glucose, blood urea nitrogen, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), bilirubin, complete blood counts (total leucocyte count, hemoglobin, hematocrit, platelets), rapid plasma reagin, HCV antibody, and flow cytometry for CD4+ T-cells were performed using standard methods. HIV RNA in plasma was quantified by RT-PCR (Roche Amplicor, version 1.5).

Statistical analysis

Means of the host, HIV, and HCV biomarkers were compared in impaired and unimpaired persons using the independent sample t-test for continuous variables and the Fisher's exact test for binary and categorical variables. Demographic characteristics and biomarkers were compared in adjusted and unadjusted analyses by univariable followed by multivariable logistic regression analysis. A p-value cut off of 0.1 at entry level and 0.05 at exit level was used in the stepwise logistic regression analysis. All statistical analyses were done using the SPSS software version 23.0.1.

Widely accepted variables associated with severity of liver disease were selected for comparison between impaired and unimpaired groups.[8] These were: a) AST to Platelet Ratio Index {APRI = [AST (IU/mL) / AST Upper limit of normal] ÷ Platelets (10^9 /ml) × 100}, b) Fibrosis-4 {FIB-4 = [Age (in years) × AST (IU/L)] ÷ [Platelet count (10^9 /L) × √ ALT level (U/L)]}0, c) albumin <4 g/dL, d) platelets <200/μL, e) AST >50 IU/L, and f) ALT >50 IU/L. Additionally, a separate variable (albumin <4g/dL and platelet <200/μL) with a composite score of 2 was created.

RESULTS

Demographic, HCV, and HIV-related characteristics

Participants were mostly middle-aged (median 46.5 years) men (77%) who were either black (44.2%) or white (39.8%) and had been diagnosed with AIDS (77%). HIV disease characteristics were similar in the impaired and unimpaired groups. The median CD4 T-cell count was 428/μL [Inter Quartile Range (IQR) 281, 628] and 55 (13%) had counts below 200/μL. After exclusion of all those with CD4 T-cell counts <200/μL, mean absolute or

square root transformed current and nadir CD4 T-cell counts did not significantly differ among the impaired and unimpaired groups. Median CD4 nadir T-cell count was 120/μL (IQR 32, 225). The mean HCV viral load was 3.5 million IU/mL without significant differences between groups (Table 1). The impaired compared with the unimpaired group was more likely to be: i) women (28% vs 17%, p = 0.008), ii) White (45% vs 31%, p = 0.001), iii) depressed (Beck depression inventory (BDI) score (15 vs 12, p<0.001)) with iv) adverse impact on basic activities of daily living (BADL, 0.8 vs 0.6, p = 0.003) and instrumental activities of daily living (IADL, 2.5 vs 1.5, p<0.001). Women were less educated than men (11.2 vs 12.4 years, p<0.001).

Liver dysfunction in impaired and unimpaired individuals

Routine laboratory and computed variables of the cohort are shown in Table 2. Variables indicative of liver injury and dysfunction found to be significantly associated with NCI were: 1) AST, 2) low albumin (<4g/dL), and 3) low platelet count (<200/μL) in combination with low albumin (Figure 1). Hemoglobin and hematocrit were lower and the International Normalized Ratio (INR), a measure of hepatic synthetic function, was higher (more abnormal) in the NCI group. Mean APRI and FIB-4 scores were higher in the impaired than the unimpaired group (p=0.009 and p=0.003, respectively) in univariable analysis (Figure 2A). None of the participants appeared to have severe liver disease as is evident from the ranges of hepatic enzymes and serum bilirubin levels (Table 2).

The results of multivariable logistic regression analysis, created by forward selection of candidate variables with p<0.10 in univariable regression, are shown in Table 3. Three candidate variables significantly and independently contributed to the model. Serum albumin <4g/dL was associated with a doubling of NCI odds compared to those with serum albumin ≥4 g/dL (OR=2, p=0.006). ALT >50 IU/L was associated with 1.7 times the odds of NCI (OR=1.68 [95% CI, 1.06–2.6], p=0.025). Similarly, for every unit increase in $\log_{10}$APRI, the odds of NCI increased by 2.2 times (OR=2.2 [95% CI, 1.01– 4.8], p=0.04).

Subgroups analyses

A univariable analysis of 347 persons with CD4 T-cell counts >200/μL and HIV RNA <50 copies/mL revealed that low serum albumin (<4g/dL) alone and in combination with low platelets (<200/μL), higher APRI and higher FIB-4 counts remained significantly associated with NCI (Figure 2B). In multivariable analysis, low platelet count (p=0.047) and higher FIB-4 (p=0.03) remained significantly associated with NCI.

HCV diagnosis based on HCV antibodies—In univariable analysis of 260 persons who were positive by HCV antibodies, low serum albumin (p=0.03), APRI (p=0.003) and FIB-4 (p=0.01) counts were significantly associated with NCI. In multivariable analysis FIB-4 (0.002) and low serum albumin in combination with low platelets (p=0.048) remained significantly associated with NCI.

HCV diagnosis based on HCV RNA—A univariable subgroup analysis of 18 persons with HCV diagnosis based on detection of RNA by PCR, higher FIB-4 was marginally

associated with NCI (p=0.05). Multivariable analysis in this subgroup did not find any significant associations between the risk factors and NCI.

To examine if these associations were driven by patients with the most abnormal values of APRI and FIB-4, the univariable analyses were repeated after exclusion of the upper 50% and upper 25% of values (Table 4). After eliminating the participants with higher values of APRI and FIB-4, values for the impaired and the unimpaired were similar. This suggests that the highest levels of hepatic inflammation and fibrosis are the major contributors to NCI.

DISCUSSION

Prevalence of NCI was 48% in HIV/HCV co-infected persons and was independently associated with low serum albumin (<4g/dL), high ALT (>50U/L), and high $\log_{10}$ APRI scores. These liver-related biomarkers suggest that the effect of HCV on brain function may be mediated through its effects on the liver. Because none of the participants had evidence of severe decompensated liver disease such as encephalopathy, bleeding or ascites, mild liver disease seems to contribute to cognitive impairment in HIV/HCV coinfection.

Numerous studies have compared the prevalence of NCI in HIV mono-infected and HIV/HCV co-infected persons with conflicting results. The prevalence of NCI (48%) in this HIV/HCV co-infected cohort is similar to that among HIV mono-infected individuals (52%) in our prior study using the same assessment methods.[1] However, because we did not include a similarly screened, recruited and contemporaneously studied group of HIV mono-infected persons, comparison of these prevalences would not be appropriate.

The higher prevalence of impairment among whites compared to other racial/ethnic groups was not expected nor is it easily explained. For example, the later presentation for care in the course of diseases for Latinos and African-Americans[9] compared to non-Hispanic whites[10], should cause them to be more rather than less impaired. Whites were significantly older than Hispanics (46.7 vs 44.0, p=0.015), a difference that could contribute to NCI, but should be adjusted for in the calculation of their expected cognitive performance. The higher prevalence of NCI in women is also seen in HIV mono-infection,[11] and may be attributable to higher rates of mental health problems, lower cognitive reserve due to less education and lower premorbid intelligence[12], or aging that have been found in other studies.[13,14]

Low serum albumin (<4 g/dL), high ALT (>50 U/L), high $\log_{10}$ APRI scores and FIB-4, four biomarkers of impaired hepatic synthetic function, damage, and fibrosis, were associated with NCI in univariable analysis. The first three variables retained in multivariable analysis, suggesting that the effect of HIV/HCV co-infection on brain function is mediated through the liver. Since none of the participants had evidence of severe liver disease, milder liver disease may contribute to cognitive impairment. To minimize the effects of HIV on NCI, only those with undetectable plasma HIV RNA (<50 copies/mL) were included in the study.

HIV/HCV coinfection may contribute to NCI and minimal hepatic encephalopathy (MHE) by at least four mechanisms. First, infection of the brain by either virus is associated with direct damage to brain tissue by neuro-toxicity and inflammation.[15] Second, chronic HIV

and/or hepatitis B or C damage the intestinal barrier resulting in translocation of bacterial components to blood causing systemic inflammation.[16,17] Third, therapy with for HCV (IFN) and HIV (efavirenz) may cause symptomatic neurotoxicity.[18] Fourth, hepatic damage or dysfunction may disable removal of toxic substances in the portal circulation or other protective mechanisms such as those attributable to low albumin as discussed below.[19]

Low serum albumin can be a consequence of either HIV or HCV infection and predicts survival in HIV[20] and HCV.[21] Serum albumin (<4 g/dL) was associated with a nearly two-fold odds of NCI in this study, but mechanisms linking low albumin to NCI are unclear. Serum albumin, a marker of liver function, acts as an antioxidant and traps free radicals in the plasma thus protecting the brain from damage due to oxidative stress.[22] Consequently, low serum albumin in the setting of oxidative stress (e.g., systemic inflammation) may enable brain damage leading to NCI in chronic HCV.[22] Low albumin was associated with poor manual dexterity and impaired visual memory in HIV/HCV co-infected subgroup in a study that compared changes in cognition in HIV mono-infected and HIV/HCV co-infected persons pre- and post-ART.[23] Low levels of serum albumin is also an independent risk factor for cognitive impairment in other diseases such as Alzheimer's disease,[24,25] heart failure,[26] HIV mono-infection[27] and also in general populations.[28]

NCI was associated with higher ALT levels (>50 U/L) in this study. Inflammation and damage to hepatocytes in chronic HCV infection elevates ALT levels. HCV infected hepatocytes, on exposure to HIV, have greater apoptosis-mediated by inflammatory cytokines.[29] Both chronic HIV and HCV elevate levels of blood biomarkers of systemic inflammation such a INF-γ, TNF-α, and IL-6.[12,30] Systemic inflammation is associated with cognitive impairment in conditions such as abdominal obesity,[31] metabolic syndrome, [32] and non-alcoholic fatty liver disease (NAFLD).[33] Thus, the findings of this study are consistent with previous reports of inflammation-mediated brain damage as the mechanism of NCI.

FIB-4 and APRI, are non-invasive, laboratory-based measures of hepatic fibrosis. Higher FIB-4 and APRI scores were more likely to be associated with NCI than lower scores at univariable level but were eliminated in the multivariable logistic regression model. After excluding the upper 25% or 50% values of FIB-4 and APRI from the analysis (Table 4), both variables were not significant aa univariable predictors of NCI suggesting that the contribution to NCI may be limited to more severe levels of liver fibrosis.

Biomarkers that were less clearly related to liver disease, but significantly associated with NCI in univariable analyses, were hemoglobin and hematocrit. Similar finding has been reported in HIV mono-infected[27] persons, but anemia as a risk factor for NCI has not been examined in HCV mono-infected individuals. WBC count, BUN, serum creatinine, HCV RNA, and C-reactive protein did not differ significantly among the cognitively impaired and unimpaired groups.

This retrospective analysis of prospectively collected research data has several limitations. First, although the HCV diagnosis was predominantly made by antibody testing, it was self-reported and not otherwise confirmed in 151 (37%) participants. The diagnosis of viremia

was made by PCR in only 18 (4.3%) participants. Since spontaneous resolution of HCV infection can occur, the cohort may have included some persons with HCV infection that had resolved. Second, no concurrently-studied HIV or HCV mono-infected controls were included. Third, details of the composition or duration of ART regimens and physical measures of liver fibrosis such as transient elastography by ultrasound were available. Another limitation in the study was unavailability of data on alcohol. Since HCV prevalence is higher in alcoholics[34] and IVDUs[35], possible confounding effects of alcohol on hepatic function[36] and cognition[37] could not be ruled out.

CONCLUSIONS

Subclinical levels of hepatic injury and dysfunction may contribute to NCI in HIV/HCV co-infected persons on optimal ART. Longitudinal studies of NCI before, during and after HCV treatment with directly-acting antivirals (DAAs) should be undertaken in both HIV-infected and uninfected persons to explore whether the cognitive impairment can be reversed. Studies of biomarkers of systemic inflammation in blood and CSF during treatment could help to clarify the mechanisms of NCI in these individuals.

Acknowledgements

We thank all the participants for their invaluable contribution.

Funding

This work was supported by the National Institute on Drug Abuse of the National Institutes of Health under the award numbers R01 DA039775 (ARB) and R01 DA16015.

Abbreviations

NCI	neurocognitive impairment
HIV	Human Immunodeficiency Virus
HCV	Hepatitis C Virus
GDS	Global Deficit Scores
HAND	HIV-Associated Neurocognitive Disorders
ART	Highly Active Antiretroviral Therapy
APRI	AST to Platelet Ratio Index
FIB-4	Fibrosis-4

REFERENCES

1. Heaton R, Clifford D, Franklin D, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology 2010; 75(23): 2087–96. [PubMed: 21135382]

2. HEATON RK, MARCOTTE TD, MINDT MR, et al. The impact of HIV-associated neuropsychological impairment on everyday functioning. Journal of the International Neuropsychological Society 2004; 10(03): 317–31. [PubMed: 15147590]

3. Kuhn T, Sayegh P, Jones JD, et al. Improvements in brain and behavior following eradication of hepatitis C. J Neurovirol 2017; 23(4): 593–602. [PubMed: 28560632]

4. Cattie JE, Letendre SL, Woods SP, et al. Persistent Neurocognitive Decline in a Clinic Sample of Hepatitis C Virus-infected Persons Receiving Interferon and Ribavirin Treatment. J Neurovirol 2014; 20(6): 561–70. [PubMed: 25326107]

5. Reported in "http://www.natap.org/2014/AASLD/AASLD_07.htm", Accessed 03/22/2018

6. Kleefeld F, Heller S, Jessen H, Ingiliz P, Kraft A, Hahn K. Effect of interferon-free therapy on cognition in HCV and HCV/HIV infection: A pilot study. Neurology 2017; 88(7): 713–5. [PubMed: 28003502]

7. Carey CL, Woods SP, Gonzalez R, et al. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. Journal of clinical and experimental neuropsychology 2004; 26(3): 307–19. [PubMed: 15512922]

8. Bharti AR, Letendre SL, Wolfson T, et al. Clinical variables identify seronegative HCV co-infection in HIV-infected individuals. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology 2011; 52(4): 328–32. [PubMed: 21924674]

9. Manly JJ, Jacobs DM, Sano M, et al. Cognitive test performance among nondemented elderly African Americans and whites. Neurology 1998; 50(5): 1238–45. [PubMed: 9595969]

10. Chen NE, Gallant JE, Page KR. A systematic review of HIV/AIDS survival and delayed diagnosis among Hispanics in the United States. Journal of immigrant and minority health 2012; 14(1): 65–81. [PubMed: 21773882]

11. Chiesi A, Vella S, Dally LG, et al. Epidemiology of AIDS dementia complex in Europe. AIDS in Europe Study Group. Journal of acquired immune deficiency syndromes and human retrovirology : official publication of the International Retrovirology Association 1996; 11(1): 39–44.

12. Keating SM, Golub ET, Nowicki M, et al. The effect of HIV infection and HAART on inflammatory biomarkers in a population-based cohort of women. Aids 2011; 25(15): 1823–32. [PubMed: 21572306]

13. Basso MR, Bornstein RA. Estimated premorbid intelligence mediates neurobehavioral change in individuals infected with HIV across 12 months. Journal of clinical and experimental neuropsychology 2000; 22(2): 208–18. [PubMed: 10779835]

14. Farinpour R, Miller EN, Satz P, et al. Psychosocial risk factors of HIV morbidity and mortality: findings from the Multicenter AIDS Cohort Study (MACS). Journal of clinical and experimental neuropsychology 2003; 25(5): 654–70. [PubMed: 12815503]

15. Forton DM, Allsop JM, Main J, Foster GR, Thomas HC, Taylor-Robinson SD. Evidence for a cerebral effect of the hepatitis C virus. Lancet 2001; 358(9275): 38–9. [PubMed: 11454379]

16. Koutsounas I, Kaltsa G, Siakavellas SI, Bamias G. Markers of bacterial translocation in end-stage liver disease. World Journal of Hepatology 2015; 7(20): 2264–73. [PubMed: 26380651]

17. Bellot P, Frances R, Such J. Pathological bacterial translocation in cirrhosis: pathophysiology, diagnosis and clinical implications. Liver international : official journal of the International Association for the Study of the Liver 2013; 33(1): 31–9. [PubMed: 23121656]

18. Mouton JP, Cohen K, Maartens G. Key toxicity issues with the WHO-recommended first-line antiretroviral therapy regimen. Expert review of clinical pharmacology 2016; 9(11): 1493–503. [PubMed: 27498720]

19. Brusilow SW. Hyperammonemic encephalopathy. Medicine 2002; 81(3): 240–9. [PubMed: 11997720]

20. Sudfeld CR, Isanaka S, Aboud S, et al. Association of serum albumin concentration with mortality, morbidity, CD4 T-cell reconstitution among tanzanians initiating antiretroviral therapy. J Infect Dis 2013; 207(9): 1370–8. [PubMed: 23319741]

21. Nagao Y, Sata M. Serum albumin and mortality risk in a hyperendemic area of HCV infection in Japan. Virology journal 2010; 7: 375. [PubMed: 21194423]

22. Oettl K, Stauber RE. Physiological and pathological changes in the redox state of human serum albumin critically influence its binding properties. British journal of pharmacology 2007; 151(5): 580–90. [PubMed: 17471184]

23. Parsons TD, Tucker KA, Hall CD, et al. Neurocognitive functioning and HAART in HIV and hepatitis C virus co-infection. Aids 2006; 20(12): 1591–5. [PubMed: 16868439]

24. Kim TS, Pae CU, Yoon SJ, et al. Decreased plasma antioxidants in patients with Alzheimer's disease. International journal of geriatric psychiatry 2006; 21(4): 344–8. [PubMed: 16534775]

25. Llewellyn DJ, Langa KM, Friedland RP, Lang IA. Serum Albumin Concentration and Cognitive Impairment. Current Alzheimer research 2010; 7(1): 91–6. [PubMed: 20205675]

26. Zuccala G, Marzetti E, Cesari M, et al. Correlates of cognitive impairment among patients with heart failure: results of a multicenter survey. The American journal of medicine 2005; 118(5): 496–502. [PubMed: 15866252]

27. Heaton RK, Franklin DR, Deutsch R, et al. Neurocognitive Change in the Era of HIV Combination Antiretroviral Therapy: The Longitudinal CHARTER Study. Clin Infect Dis 2015; 60(3): 473–80. [PubMed: 25362201]

28. Ng TP, Niti M, Feng L, Kua EH, Yap KB. Albumin, apolipoprotein E-epsilon4 and cognitive decline in community-dwelling Chinese older adults. Journal of the American Geriatrics Society 2009; 57(1): 101–6. [PubMed: 19054180]

29. Jang JY, Shao RX, Lin W, et al. HIV infection increases HCV-induced hepatocyte apoptosis. J Hepatol 2011; 54(4): 612–20. [PubMed: 21146890]

30. Zampino R, Marrone A, Restivo L, et al. Chronic HCV infection and inflammation: Clinical impact on hepatic and extra-hepatic manifestations. World Journal of Hepatology 2013; 5(10): 528–40. [PubMed: 24179612]

31. Sattler FR, He J, Letendre S, et al. Abdominal obesity contributes to neurocognitive impairment in HIV-infected patients with increased inflammation and immune activation. J Acquir Immune Defic Syndr 2015; 68(3): 281–8. [PubMed: 25469522]

32. Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. Jama 2004; 292(18): 2237–42. [PubMed: 15536110]

33. Seo SW, Gottesman RF, Clark JM, et al. Nonalcoholic fatty liver disease is associated with cognitive function in adults. Neurology 2016; 86(12): 1136–42. [PubMed: 26911638]

34. Bruguera M, Forns X. [Hepatitis C in Spain]. Med Clin (Barc) 2006; 127(3): 113–7. [PubMed: 16828003]

35. Alter MJ. Epidemiology of hepatitis C virus infection. World journal of gastroenterology 2007; 13(17): 2436–41. [PubMed: 17552026]

36. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology 2011; 141(5): 1572–85. [PubMed: 21920463]

37. Sachdeva A, Chandra M, Choudhary M, Dayal P, Anand KS. Alcohol-Related Dementia and Neurocognitive Impairment: A Review Study. International journal of high risk behaviors & addiction 2016; 5(3): e27976. [PubMed: 27818965]

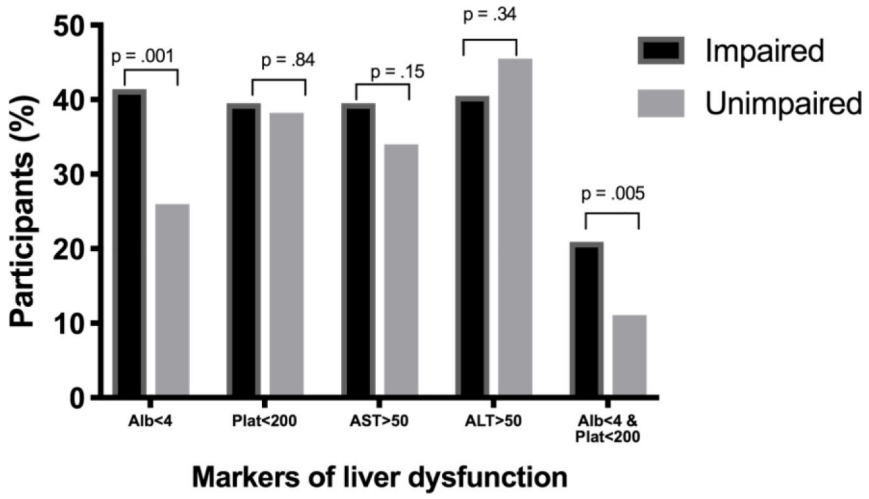

Figure 1.

Neurocognitive impairment by markers of liver dysfunction. NCI was associated with low serum albumin (<4g/dL) alone and in combination with platelets <200/μL. [Alb: albumin; Plat: platelets; AST-aspartate aminotransferase; ALT- alanine aminotransferase

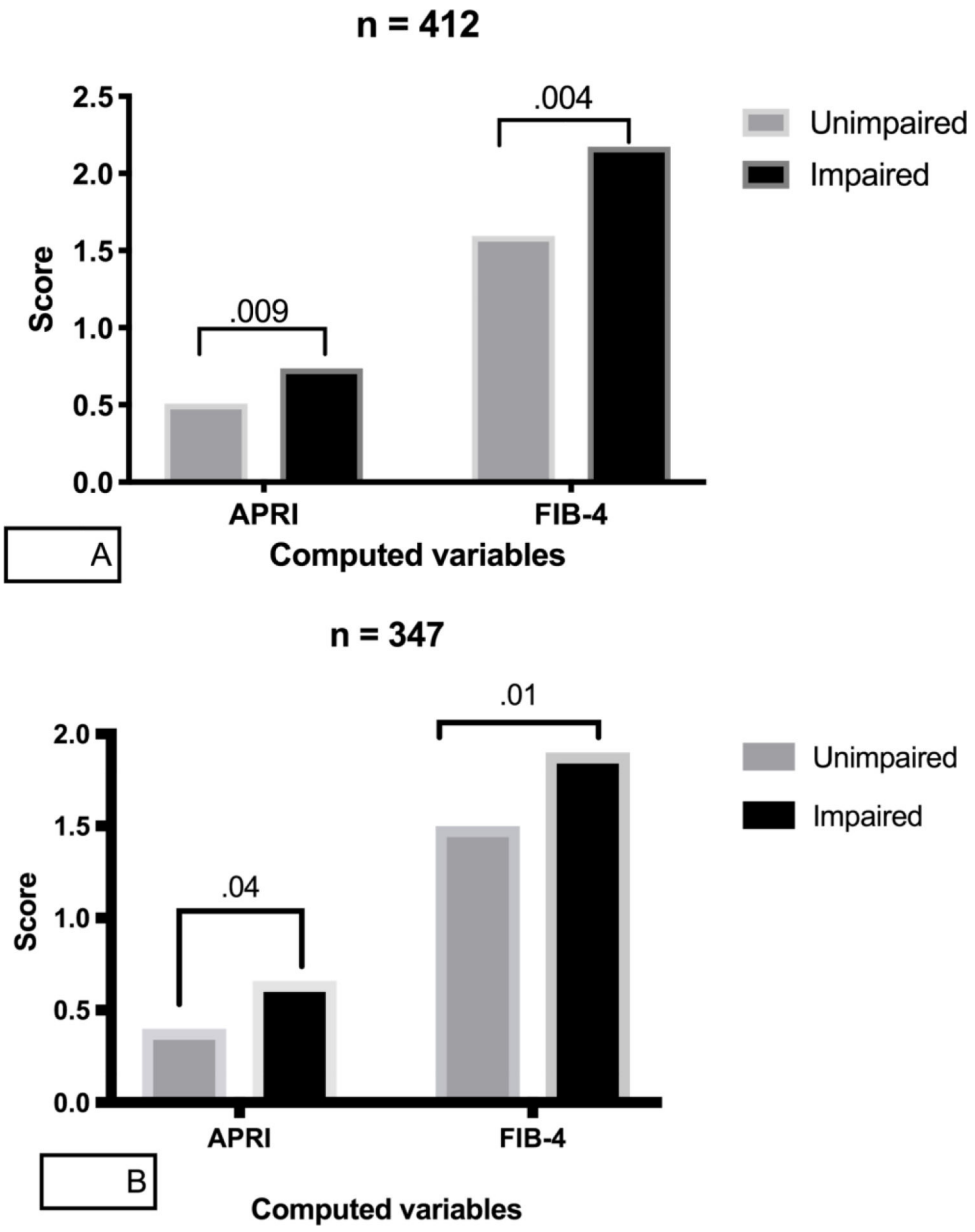

Figure 2.

Neurocognitive impairment by computed variables: APRI and FIB-4. 2A: In the entire cohort (n=412). 2B: In a subgroup with CD4 T-cell counts >200/μL and HIV RNA <50 copies/mL (n=347). In both instances, mean APRI and FIB-4 scores were higher in the impaired than the unimpaired group. [APRI: AST to Platelet Ratio Index; FIB-4: Fibrosis-4]

Table 1.

Demographic and disease characteristics of HIV/HCV co-infected persons with and without NCI.

Variables	Total Cohort	Impaired (n = 198)	Unimpaired (n = 214)	p-value
	Mean±SD or n (%)	Mean±SD or n (%)	Mean±SD or n (%)	
Age (years)	46.6±7.7	46.9±1.8	46.9±6.8	0.4
Gender (Male)	319 (77%)	142 (72%)	177 (82.7%)	0.008
Education (years)	12±2.5	12.8±2.7	12±2.4	0.09
Ethnicity				0.001
Asian	3 (0.12%)	3 (1.5%)	0 (0)	
Black	182 (44.2%)	67 (33.8%)	115 (53.7%)	
Hispanic	58 (14%)	33 (16.6%)	25 (11.6%)	
White	164 (40%)	91 (45%)	73 (31.1%)	
Other	5 (1.2%)	4 (2.2%)	1 (0.46%)	
BDI[1]	13±10.7	15.4± 10.5	11.5±10.5	<0.001
% with BDI >17	134(33%)	83(42%)	51(24%)	<0.001
IADL[2]	2±2.4	2.5±2.6	1.5±2	<0.001
BADL[3]	0.75±0.9	0.8±0.9	0.6±.8	0.003
Employment	79(19%)	34(17.20%)	45(21.5%)	0.08
% with Plasma HIV <50c/mL	412(100%)	198(100%)	214(100%)	0.5
Current CD4$^+$ cells/±L M(IQR)	428(281–628)	436 (264–651)	413 (286–605)	0.22
Nadir CD4$^+$cells/±L M(IQR)	120 (32–225)	120 (30–222)	123 (35–227)	0.5
Diabetes mellitus	60 (14%)	30 (15%)	30 (14%)	0.9
PWID[4]	162 (39%)	82 (41%)	80 (37%)	0.7
BMI[5]	26.2±4.8	26.2±5.1	26.3±4.6	0.8
HCV diagnosis				
Self-report	151 (37%)	68 (34%)	83 (38%)	0.2
HCV Ab	243 (59%)	118 (60%)	125 (59%)	0.2
HCV RNA	18 (4%)	12 (6%)	6 (3%)	0.2
AIDS diagnosis	318 (77%)	152 (77%)	166 (77%)	0.9
Duration of HIV infe ction (years)	11.3±6.3	11.7±6.3 (n = 185)	11.6±6.4	0.8

[1] BDI: Beck Depression Inventory

[2] IADL: Instrumental Activities of Daily Living Complaints

[3] BADL: Basic Activities of Daily Living

[4] PWID: people who inject drugs and mixed-race participants

[5] BMI: Body Mass Index

Table 2.

Laboratory and computed variables in impaired and unimpaired participants

Measured Variables	Impaired		Unimpaired		p-value
	Range	Mean ± SD	Range	Mean ± SD	
Hemoglobin g/dL	9.3–17.6	13.6±1.5	8.6–18.6	13.9±1.5	0.02
Hematocrit (%)	27–49	40±4.4	30–55	41±4.3	0.02
WBC10^3/μL	1.4–13.4	5.4± 2	15–9.5	5.2±0.16	0.28
Platelets ×10^3/μL	33–497	217±82	64–459	222±69.4	0.62
INR	1–1.1	1.1±0.07	1–1.1	1±0.0	0.05
AST IU/L	13–407	58±49	9–184	48± 28	0.04
ALT IU/L	11–321	60±55	9–396	56±43	0.9
Bilirubin mg/dL	1–4.2	0.82±0.73	1–5	0.85±0.73	0.7
Albumin g/dL	1–3.9	4±0.56	2.5–5	4.2±0.4	0.005
BUN mg/dL	3–38	14.24±7.3	5–46	13.71±53	0.4
Creatinine mg/dL	0.4–13	1.08±0.08	0.57–7	1±0.03	0.3
Computed Variables, n (%) or Mean ± SD					
Albumin <4 g/dL	79 (41%)		55 (26%)		0.001
Platelets <200 ×10^3/μL	75 (39%)		79 (38%)		0.8
Albumin <4 g/dL and Platelets <200 ×10^3/μL	40 (21%)		23 (11%)		0.005
AST >50 IU/L	75 (39.5%)		70 (34%)		0.1
ALT >50 IU/L	75 (40.5%)		92 (45.5%)		0.3
APRI	0.73±1.13		0.50±0.40		0.009
FIB-4	2.17±2.14		1.59±1.09		0.003

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; BUN: Blood Urea Nitrogen; APRI: AST to Platelet Ratio Index; FIB-4: Fibrosis-4 Score

Table 3.

Multivariable logistic regression analysis

Covariate	Adjusted OR	Adjusted p-value
Albumin <4 g/dL	1.9 (1.2, 2.8)	0.006
ALT >50 IU/L	1.7 (1.06, 2.64)	0.02
Log_{10}APRI	2.2 (1.01, 4.8)	0.04

Table 4:

Sub-group analysis of FIB-4 and APRI after excluding the upper 25% and 50%

	FIB-4 after exclusion						
	Impaired			Unimpaired			p-value
	N	Mean	SD	N	Mean	SD	
Upper 25%	152	1.35	0.5	180	1.25	0.5	0.38
Upper 50%	83	0.92	0.24	99	0.87	0.85	0.49
	APRI after exclusion						
Upper 25%	166	0.44	0.26	196	0.044	0.25	0.94
Upper 50%	137	0.34	1.4	161	0.34	1.4	0.95