Neurocognitive functioning and HAART in HIV and hepatitis C virus co-infection

Thomas D. Parsons, Karen A. Tucker, Colin D. Hall, Wendy T. Robertson, Joseph J. Eron, Michael W. Fried and Kevin R. Robertson

Objectives: This study examined the effects of HAART on neurocognitive functioning in persons with hepatitis C virus (HCV) and HIV co-infection.

Design: A prospective study examining neurocognitive performance before and after HAART initiation.

Method: Participant groups included a mono-infected group (45 HIV+/HCV− participants) and a co-infected group (20 HIV+/HCV+ participants). A neuropsychological battery (attention/concentration, psychomotor speed, executive functioning, verbal memory, visual memory, fine motor, and gross motor functioning) was used to evaluate all participants. After 6 months of HAART, 31 HIV+ mono-infected and 13 HCV+/HIV+ co-infected participants were reevaluated.

Results: Neurocognitive functioning by domain revealed significantly worse performance in the co-infected group when compared to the monoinfected group on domains of visual memory and fine motor functioning. Assessment of neurocognitive functioning after antiretroviral therapy revealed that the co-infected group was no longer performing worse than the monoinfected group.

Conclusions: The findings of the current study suggest that persons with HCV+/HIV+ co-infection may have greater neurocognitive declines than persons with HIV infection alone. HCV+/HIV+ co-infection may accelerate the progression of HIV related neurocognitive decline.

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Introduction

Epidemiological data from recent large-scale studies on the rate of hepatitis C virus (HCV) and HIV co-infection suggest that about one-third of all persons infected with HIV are co-infected with HCV [1]. In addition to the common risk factors and routes of transmission in HIV and HCV, co-infected patients may have an accelerated course of medical and neurocognitive complications [2,3]. Unique and similar routes of transmission are found in HIV [4,5] and HCV [6]. Further, similar neurocognitive deficits are apparent in HIV and HCV [7]. The frontal–subcortical pattern of neurocognitive deficits in HIV-infected persons is similar to that found in HCV-infected persons, with deficits in complex attention/concentration and information processing and

University of North Carolina, Chapel Hill, North Carolina, USA.
Correspondence to T. D. Parsons, Department of Neurology, CB # 7025, University of North Carolina School of Medicine, 3114 Bioinformatics Building, Chapel Hill, NC 27599-7025, USA.
Tel: +1 919 966 8172; fax: +1 919 966 2922; e-mail: tparsons@neurology.unc.edu
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psychomotor speed [8–11]. Additionally, studies of HCV infection have revealed declines in visual recognition memory [12]. Changes in reaction time associated with HCV [13] have also been linked to depressive symptoms [14] and secondary effects of treatment with interferon-alpha [15–18]. Findings from studies of HIV and HCV co-infection have revealed greater neurocognitive impairment in co-infected patients on measures of executive and overall cognitive functioning [19–21].

The purpose of the current study was to examine the neurocognitive functioning in HIV/HCV co-infected patients before and after antiviral therapy compared to patients with HIV alone. Study hypotheses included that: neurocognitive performance would be worse in co-infected patients when compared with mono-infected patients; neurocognitive performance of both co-infected and mono-infected groups was expected to increase following 6 months of antiviral therapy.

Method

Participants

Participant groups included a mono-infected group (45 HIV+/HCV− participants) and a co-infected group (20 HIV+/HCV+ participants). Participant from each group were recruited from the University of North Carolina (UNC) Healthcare System. All procedures were explained to the participants and written informed consent was obtained in a manner approved by the UNC Institutional Review Board. Comparable HIV severity within each stage was found for the two groups (mono-infected: 23.4% asymptomatic, 14.9% symptomatic, 61.7% AIDS; co-infected: 19% asymptomatic, 14.3% symptomatic, 66.7% AIDS). Exclusion criteria included a history of neurological conditions that may affect non-neuroAIDS related neurocognitive functioning. Due to finding fewer years of education and more African–Americans in the co-infected group than in the mono-infected group, analyses were adjusted for possible differences related to these variables. Demographic characteristics of the mono-infected and co-infected groups are shown in Table 1.

While analysis revealed that current substance use (alcohol, cocaine, and cannabis) was infrequent and similar for both groups, self-report of past substance abuse was significantly greater for cocaine and heroin use in the co-infected than in the mono-infected group. No significant group differences were found for past history of other stimulants, opiates, sedative-hypnotics,

Table 1. Demographic and clinical characteristics of mono-infected and co-infected study participants.

	Mono-infected ($n = 45$)	Co-infected ($n = 20$)	P
Demographics			
Age (years) [mean (SD)]	40.0 (6.8)	42.8 (4.9)	ns
Male (%)	68	60	ns
African–American (%)	66	90	0.04
Years of education	13.1 (2.1)	11.5 (2.1)	0.006
HIV characteristics			
CD4 T-cell count (cells/μl) [mean (SD)]	267.9 (222.1)	217.5 (170.7)	ns
Plasma HIV RNA (log copies/μl)	4.2 (1.6)	4.3 (1.8)	ns
Liver function			
Alanine aminotransferase (U/l) [mean (SD)]		65.0 (43.9)	
Aspartate aminotransferase (U/l) [mean (SD)]		56.5 (38.3)	high
Alkaline phosphatase (U/l) [mean (SD)]		98.1 (37.5)	
Albumin (g/dl)		3.6 (0.5)	
Total protein (g/dl)		7.7 (1.1)	
Total bilirubin (mg/dl)		0.4 (0.3)	
Past substance use (%)			
Alcohol treatment	14.9	30.0	ns
History of DUI	17.0	25.0	ns
Cocaine	59.6	90.0	0.01
Other stimulants	23.4	40.0	ns
Opiates	12.8	15.0	ns
Heroin	12.8	35.0	0.04
Sedative–hypnotic	17.0	20.0	ns
Hallucinogens	23.4	35.0	ns
Cannabis	83.0	75.0	ns
Current substance use [mean (SD)]			
Alcohol (drinks/month)	13.6 (74.4)	18.4 (44.9)	ns
Cocaine (days/month)	0.21 (0.9)	1.6 (6.7)	ns
Cannabis (days/month)	1.2 (4.5)	0.5 (1.2)	ns
Current psychiatric (%)			
Depression	33.3	33.3	ns
Anxiety	35.6	33.3	ns

Mono-infected subjects were HIV seropositive; co-infected subjects were positive for HIV and HCV. Categorical variables were analyzed with Chi-Square analyses. Continuous variables were analyzed with t tests. DUI, Driving under the influence; HCV, hepatitis C virus; ns, not significant.

hallucinogens, cannabis, or alcohol abuse treatment. Depression and anxiety were reported in approximately one-third of each group. Clinical characteristics of the mono-infected and co-infected groups are shown in Table 1.

Neuropsychological evaluation

Neurocognitive evaluations were performed before and after 6 months of antiretroviral therapy: attention/concentration (2 and 7 test, PASAT), psychomotor speed (computerized simple and choice reaction time tasks, Digit Symbol, Trails A, Stroop Word), executive functioning (Trails B, Stroop Color-Word), verbal memory (Auditory Verbal Learning Test), visual memory (Complex Figure Test: Immediate Memory, Delayed Recall), fine motor speed (Grooved Pegboard, Finger Tapping), and gross motor functioning (timed gait). The tests comprising each of the domains were converted to z scores and averaged to obtain a score for each of the domains as described in previous HIV studies [8].

Results

Mixed model analyses did not reveal significant results for the interaction between groups in the neuropsychological total z score before and after antiretroviral treatment ($F_{1,45} = 2.63$; $P = 0.11$). Mixed model analyses of neurocognitive functioning by domain revealed significantly worse performance in the co-infected group when compared to the monoinfected group on domains of visual memory ($F_{1,45} = 10.53$; $P < 0.002$) and fine motor functioning ($F_{1,45} = 12.14$; $P < 0.001$). Mixed model analyses of neurocognitive functioning by domain before and after antiretroviral therapy revealed that the co-infected group was no longer performing significantly worse than the monoinfected group on the domain of visual memory ($F_{1,45} = 3.95$; $P = 0.053$) and in fine motor functioning there was little difference between the groups ($F_{1,45} = 0.01$; $P < 0.92$). See Table 2 for mixed model results for mono-infected and co-infected groups before and after HAART.

Table 2. Mixed model results for mono-infected and co-infected groups before and after HAART.

	Mono-infected [least mean square (SE)][a]	Co-infected [least mean square (SE)][a]
Baseline		
Neurocognitive Summary Score	−0.64 (0.10)	−0.92 (0.14)
CD4 T-cell count (cells/μl)	261.99 (30.663)	217.45 (46.5733)
Plasma HIV RNA (log copies/μl)	4.24 (0.24)	4.26 (0.36)
Following HAART		
Neurocognitive Summary Score	−0.57 (0.10)	−0.53 (0.17)
CD4 T-cell count (cells/μl)	317.13 (32.23)	316.77 (50.94)
Plasma HIV RNA (log copies/μl)	3.20 (0.27)	3.06 (0.45)

[a]At baseline $n = 45$ for the monoinfected group and $n = 20$ for the co-infected group; after HAART $n = 31$ for the monoinfected group and $n = 13$ for the co-infected group.

Given the greater likelihood that the HCV+/HIV+ co-infected group would have a past history of substance abuse (cocaine and heroin), one way ANOVA were utilized to assess their possible influence. Neurocognitive functioning between those with a substance abuse history (cocaine and heroin) and those without this history was not significantly different. Further, assessment of liver function data revealed that decreased albumin level scores were related to poorer psychomotor speed (r, 0.58; $P = 0.09$), overall performance (r, 0.46; $P = 0.04$), and attention and concentration (r, 0.48; $P = 0.03$). A relationship was also found between decrease in total protein value and psychomotor speed decline (r, 0.51; $P = 0.03$).

Given the 35% attrition rate in both groups, further analyses were performed to assess differences between a 'dropout' group and a 'retained' group following antiretroviral therapy. Mono-infected participants who remained in the study were significantly older than those who dropped out of the study (retained group: mean age, 41.4 years; SD, 6.2; dropout group: mean age, 37.3 years, SD, 7.3; $P = 0.05$). There were no differences, however, in mono-infected participants' baseline neurocognitive performance among those in the dropout group and those in the retained group. Although there were no demographic differences between the co-infected participants in the retained and dropout groups, a significant difference was found on the visual memory measure with the dropout group outperforming the retained group (retained group: mean, −2.1; SD, 0.89; dropout group: mean score, −1.1; SD, 1.19; $P = 0.04$). Comparisons of the dropout group with the retained group revealed no immunologic or virologic differences in either the mono-infected or co-infected groups.

Discussion

The results of this study revealed that prior to antiretroviral therapy, HCV+/HIV+ co-infected participants had significantly poorer visual memory and manual dexterity than did the HIV+ mono-infected participants. Results also showed that co-infection accounted for 20% of this variance. These findings are suggestive of a higher risk for the development of neurocognitive dysfunction among HCV+/HIV+ co-infected persons.

A greater percentage of HCV+/HIV+ co-infected participants performed poorly on neurocognitive tasks: visual memory (co-infected, 75%; mono-infected, 47%); fine motor speed (co-infected, 60%; mono-infected,

23%); neuropsychology summary score (co-infected, 50%; mono-infected, 20%). Though the neurocognitive changes following treatment with HAART did not reach significant levels, there was a general trend for improvement in the co-infected group. This suggests that the neurocognitive difficulties associated with HCV may be amenable to treatment with antiretroviral therapy, and the co-infected subjects may have increased benefit from antiretroviral therapy.

Current study results revealing decreased manual dexterity and inferior memory for visually presented information in the co-infected sample are consistent with the findings of Hilsabeck *et al.* who found a reduction in visual recognition memory, attention, and psychomotor speed in a HCV sample [12]. Correspondingly, findings from the current study that declining albumin values are associated with poorer manual dexterity and inferior visual memory are suggestive of a relationship between deteriorated liver function and decreased attentional and psychomotor functions. However, Ryan *et al.* found significant differences in executive functioning related to HCV status [21], the current study did not. A possible reason for this discrepancy is that Ryan *et al.* administered a more demanding assessment of executive functioning than the one utilized in the current study.

Current study results were suggestive of difficulties with neurocognitive tasks requiring processing of visual information among patients with HCV. These findings are consistent with those of Hilsabeck *et al.* in a HCV sample [12]. Deficient visual information processing in HCV patients may be due to treatment with pegylated interferon, as there have been reports of visual changes associated with this treatment [22,23]. Future studies should assess for the possible contribution of interferon treatment by examining HCV patients before and after treatment. Further, the more extensive changes in fine motor speed found in co-infected patients, may in part be reflective of metabolic abnormalities in the basal ganglia for persons with HCV and/or HIV [9]. Hence, HCV+/HIV+ co-infection may result in more manifest basal ganglia changes, resulting in additional motor speed declines.

It is important to note that the interpretation of the current study's findings may be vulnerable to a 35% dropout rate for both groups. Although this study statistically controlled for racial composition and educational level across groups, future studies should be attempted in which groups of subjects with matched demographics are included. Additionally, future studies should make similar comparisons with HCV+/HIV+ co-infection, HCV mono-infection, and healthy controls. A further possible limitation is that of practice effects influencing the performance of the co-infected group on the visual memory task. This, however, seems unlikely to account for all of the variance in the significant changes found in this study. Alternate versions were employed in the visual memory assessment, which contained dissimilar stimuli at baseline to those used following antiretroviral therapy. Moreover, there was a slight decrease in the monoinfected group's performance. This is contra the expected increase following treatment if repeated testing resulted in practice effects. Future prospective studies are needed to examine the extent to which HCV may accelerate the progression of neurological changes in HIV leading to neurocognitive decline.

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