Liver Fibrosis Linked to Cognition in HIV and HCV: The Women's Interagency HIV Study

Victor G. Valcour MD[1], Leah H. Rubin PhD[2], Mary U. Obasi BA[1], Pauline M. Maki PhD[2,3], Marion G. Peters MD[4] , Susanna Levin NP[5], Howard A. Crystal MD[6], Mary A. Young MD[7], Wendy J. Mack PhD[8], Mardge H. Cohen MD[9], Christopher B. Pierce MHS[10], Adaora A. Adimora MD[11,12], Phyllis C. Tien MD[13,14] for the Women's Interagency HIV Study protocol team

UCSF Memory and Aging Center
Department of Neurology

[1]Memory and Aging Center, Sandler Neurosciences Center, University of California, San Francisco, CA. [2]Department of Psychiatry, University of Illinois at Chicago, Chicago, IL. [3]Department of Psychology, University of Illinois at Chicago, Chicago, IL. [4]Division of Gastroenterology, Department of Medicine, University of California San Francisco San Francisco, CA. [5]Montefiore Medical Center, The University Hospital for the Albert Einstein College of Medicine, Department of Medicine, Women's Interagency HIV Study, Bronx. [6]Department of Neurology, SUNY Downstate, Brooklyn, NY. [7]Georgetown University Medical Center Washington, DC. [8]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA. [9]Department of Medicine, Stroger Hospital and Rush Medical Center, Chicago, IL. [10]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, MD. [11]Department of Medicine, UNC School of Medicine, Chapel Hill, NC. [12]Department of Epidemiology, UNC Gillings School of Global Public Health, Chapel Hill, NC. [13]Department of Medicine, University of California San Francisco, San Francisco, CA. [14]Department of Veterans Affairs Medical Center, Infectious Disease Section, San Francisco, CA.

Background

- Cognitive impairment is prevalent in HIV despite access to effective combination antiretroviral therapy.
- "Subclinical" Hepatic Encephalopathy, or Minimal Hepatic Encephalopathy (MHE), occurs intermittently in cirrhotic patients who appear normal except for neuropsychological (NP) test abnormalities.
  - Commonly impaired domains: psychomotor speed, information processing, attention or vigilance
- These neuropsychological deficits are similar to those observed among individuals with HIV-associated neurocognitive disorders.
- Hypothesis: Both the inflammation and loss of gut protective barriers associated with chronic HIV infection could add risk for MHE. If so, liver fibrosis in the absence of cirrhosis will correlate with neuropsychological testing performance.

Methods

- A cross-sectional investigation of liver fibrosis severity in women from the Women's Interagency HIV Study (WIHS, n=1479)
- Liver fibrosis by aspartate aminotransferase to platelet ratio index, APRI). Significant fibrosis defined as APRI >0.5 (commonly accepted definition for moderate or severe fibrosis)
- A confirmatory analysis measured liver fibrosis by FibroScan® transient elastography (n=303)
- A neuropsychological battery was designed to capture domains impacted by HIV infection.
- HIV status was confirmed by ELISA, and re-confirmed with western blot assays.
- Hepatitis C (HCV) status was defined using antibody testing and confirmatory HCV RNA testing, when available.
- We used multivariable linear regression to evaluate the independent contributions of HIV and HCV to cognitive functioning in a model that included fibrosis plus key confounding variables.

	Fibrosis		
Background Characteristics (%)	Significant (n=258)	Not Significant (n=1221)	p-value
Age, mean (SD)	51 (7.25)	45 (9.37)	<0.001
Years of education, mean (SD)	12 (2.68)	13 (2.91)	<0.001
HIV status, %	217 (84)	788 (64)	<0.001
Race/Ethnicity			0.04
African American, non-Hispanic	153 (60)	794 (65)	
White, non-Hispanic	34 (13)	148 (12)	
Hispanic	65 (25)	227 (18)	
Other	6 (2)	52 (4)	
HIV Disease[†]			
Nadir CD4 count, median (IQR)	176 (131)	226 (165)	<0.001
CD4 Count			
> 500	75 (34)	432 (55)	<0.001
≥ 200 and < 500	95 (44)	270 (34)	
< 200	47 (22)	86 (11)	
Plasma HIV RNA			<0.001
Undetectable	92 (42)	437 (55)	
< 10,000	73 (34)	259 (33)	
≥ 10,000	52 (24)	92 (12)	
cART >95% compliance	135 (62)	501 (63)	0.86
APRI, median (IQR)	1.34 (0.68)	0.23 (0.14)	<0.001

Table 1: Demographic Characteristics for participants

Figure 1: Relationships of HIV and HCV status to liver fibrosis

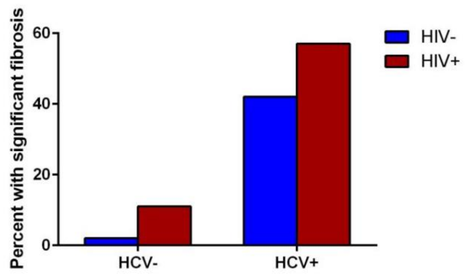
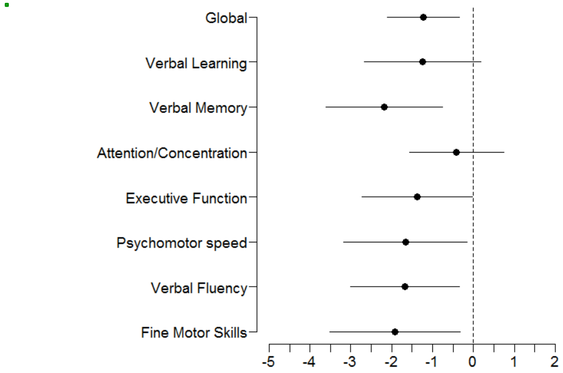


Figure 2: Independent contributions of fibrosis on cognitive test performance, adjusted for HIV, HCV, and confounders



Main effects of fibrosis noted on global cognition, verbal memory, executive functioning, psychomotor speed, verbal fluency, and fine motor skills

Figure 3: Independent contributions of HIV on cognitive test performance, adjusted for HCV, fibrosis and confounders

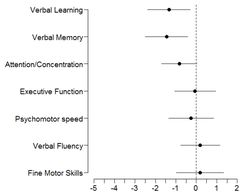
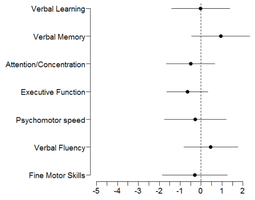


Figure 4: Independent contributions of HCV on cognitive test performance, adjusted for HIV, fibrosis and confounders



Results

- Significant fibrosis (APRI >0.5) was associated with worse performance on global cognition and multiple individual cognitive domains: verbal learning, executive function, verbal memory, psychomotor speed, fluency, and fine motor skills.
- In models adjusted for fibrosis, smaller associations were found for verbal learning and memory domains in HIV
- We found no effect for HCV on the domain scores; although minor effects were noted on two individual tests in attention and executive functioning domains in relation to HCV
- In a confirmatory analysis using FibroScan® (n=303), we generally found similar findings with significance in domains of attention, executive functioning, & fluency.

Conclusions

- Significant liver fibrosis is associated with worse neuropsychological testing performance independent of both HIV and HCV status.
- These findings are particularly important for HCV/HIV dual-infected individuals due to high burden of fibrosis.
- The pattern of cognitive impairment identified is not typical of that reported in MHE, raising suspicion for alternative mechanisms (e.g. general inflammation).
- Potential Clinical Implications:
  - In this group, APRI >0.5 was a more useful marker of risk for cognitive impairment than HCV status..
  - We identified possible non-HIV-specific contributions to cognitive impairment in HIV+ patients.

Data were collected by the Women's Interagency HIV Study (WIHS) Collaborative Study Group with centers (Principal Investigators) at New York City/Bronx Consortium (Kathryn Anastos); Brooklyn, NY (Howard Minkoff and Deborah Gustafson); Washington, DC, Metropolitan Consortium (Mary Young); The Connie Wofsy Study Consortium of Northern California (Ruth Greenblatt, Bradley Aouizerat, and Phyllis Tien); Los Angeles County/Southern California Consortium (Alexandra Levine and Marek Nowicki); Chicago Consortium (Mardge Cohen); Data Coordinating Center (Stephen Gange and Elizabeth Golub). This work was supported by a minority supplement to Mary Obasi from NIH