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FIB-4 values and neurocognitive function in HIV-infected patients without hepatic coinfections

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ABSTRACT:

— ***Introduction:*** HIV-infected patients, even if successfully treated, are at increased risk of neurocognitive impairment. Altered neuropsychological performance and neurocognitive impairment are frequently reported in patients with chronic HCV infection, often at stages characterized as having a lack of significant liver fibrosis and cirrhosis. A recent study suggests that FIB-4 index at cART initiation, and its modification over time are risk factors for major liver-related events and death, independently of infection with HCV.

— ***Purpose of the study:*** We investigated the relationship between FIB-4 values and neurocognitive performance in HIV-infected patients without HCV and/or HBV coinfection.

— ***Patients and Methods:*** We enrolled consecutive HIV-infected outpatients. In each patient demographic, clinical and therapeutic characteristics were recorded from clinical records. Each patient underwent a complete neurocognitive assessment with a battery of 8 tests: Trail Making Test-A (TMT-A), Trail Making Test-B (TMT-B), Digit Span (DSp), immediate (Rey 15) and delayed (D-Rey 15) recall of Rey's 15, Digit Symbol (DSy), Letter fluency test (Flu), Rey complex figure (R-Fig). We also considered 2 global z-score NPZ-4 (TMA-Z+TMB-Z+DSp-Z+DSy-Z) and NPZ-8 (TMA-Z+TMB-Z+DSp-Z+DSy-Z+15-Z+15dif-Z+Flu-Z+FigR-Z). FIB-4 was also calculated considering values <1.45 were indicative of low level of hepatic fibrosis, values between 1.46 and 3.25 of moderate fibrosis and values >3.25 of advanced fibrosis. Patients with HCV and/or HBV hepatic coinfection were excluded.

— ***Results:*** we enrolled 52 HIV-infected patients with a median age of 44 (IQR 38.5-50), 33 (63.4%) were males and 29 (55.7%) heterosexuals. Twelve (23%) had a previous AIDS diagnosis. Median CD4 cells count was 793 (IQR 616-1231.5) cells/mm3 and 46 (88.5%) had an undetectable HIV RNA. According to FIB-4 results, 48 (92.3%) patients had values <1.45 and 4 (7.7%) between 1.46 and 3.25 (26.2%), no patient had a value >3.25. Median FIB-4 value was 0.85 (IQR 0.70-1.06).FIB-4 levels were significantly correlated with longer duration of known HIV infection (Rho=0.29, p<0.05) and longer cART exposure (Rho=0.36, p<0.05) whereas no correlation was evidenced with level of education, previous AIDS diagnosis, CD4 cell nadir, current CD4 count, negative HIV RNA, NPZ-4 and NPZ-8 results.

— ***Conclusions:*** Most HIV mono-infected patients had a fully suppressed HIV RNA and FIB-4 values consistent with low levels of hepatic fibrosis. Higher FIB-4 results were significantly correlated with longer HIV infection and cART duration but not with neurocognitive performance, suggesting a dissociation between long-term hepatic toxicity and neuroprotective function of antiretrovirals.

— ***Keywords:*** HIV, FIB-4, Neurocognitive impairment.

INTRODUCTION

HIV-infected patients and HIV/HCV co-infected, even if successfully treated, are at increased risk of neurocognitive impairment[1,2]. Altered neuropsychological performance and neurocognitive impairment also are frequently reported in patients with chronic HCV infection, often at stages characterized as having a lack of significant liver fibrosis and cirrhosis[3]. A recent study suggests that FIB-4 index at cART initiation, and its

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modification over time are risk factors for major liver-related events and death, independently of infection with HCV and could be used to monitor HIV-infected patients on cART[4].

PATIENTS AND METHODS

We enrolled consecutive HIV-infected out-patients. In each patient demographic (including the level of education), clinical (previous AIDS, current CD4 count, CD4 nadir) and therapeutic characteristics were recorded from clinical records.

Each patient underwent a complete neurocognitive assessment with a battery of 8 tests: Trail Making Test-A (TMT-A), Trail Making Test-B (TMT-B), Digit Span (DSp), immediate (Rey 15) and delayed (D-Rey 15) recall of Rey's 15, Digit Symbol (DSy), Letter fluency test (Flu), Rey complex figure (R-Fig).

We also considered 2 global z-score NPZ-4 (TMA-Z+TMB-Z+DSp-Z+DSy-Z) and NPZ-8 (TMA-Z+TMB-Z+DSp-Z+DSy-Z+15-Z+15dif-Z+Flu-Z+FigR-Z).

FIB-4 index was calculated with the following formula[5]:

$$\text{FIB-4} = \frac{\text{Age (years) X AST (U/L)}}{\text{Platelet count } (10^9/\text{L}) \text{ X [ALT (U/L)]}}$$

The resulting values were employed both as a continuous variable and divided into categories as follows: FIB-4 value >3.25 as a proxy for advanced fibrosis; FIB-4 value between 1.45 and 3.25 in which fibrosis status is considered as undetermined; FIB-4 value <1.45 considered as mild fibrosis or absence of significant fibrosis. Patients with HCV and/or HBV hepatic co-infection were excluded.

The aim of our study was to investigate the relationship between FIB-4 values and neurocognitive performance in HIV-infected patients without HCV and/or HBV coinfection.

RESULTS

We enrolled 52 HIV-infected patients with a median age of 44 (IQR 38.5-50), 33 (63.4%) were males and 29 (55.7%) heterosexuals. Twelve (23%) had a previous AIDS diagnosis. Median CD4 cells count was 793 (IQR 616-1231.5) cells/mm^3, median nadir CD4 was 278.5 (IQR 161-385) cells/mm^3 and 46 (88.5%) had an undetectable HIV RNA. Seven (13.4%) patients had a previous clinical diagnosis of lipodystrophy. A total of 30 (57.7%) patients were receiving non-nucleoside reverse transcriptase inhibitors (NNRTI)-based, 16 (30.8%) protease inhibitors (PI)-based and 6 (11.5%) INI (integrase inhibitors)-based regimens.

According to FIB-4 results, 48 (92.3%) patients had values <1.45 and 4 (7.7%) between 1.46 and 3.25 (26.2%), no patient had a value >3.25. Median FIB-4 value was 0.85 (IQR 0.70- 1.06).

Given the low number of patients with FIB-4 higher than 1.46 the variable was only considered as continuous and Spearman rho correlation coefficient was calculated to explore significant correlations with other variables of interest (level of education, previous AIDS, CD4 count, negative HIV RNA

FIB-4 levels were significantly correlated with longer duration of known HIV infection (rho=0.29, $p<0.05$) and longer cART exposure (Rho=0.36, $p<0.05$) whereas no correlation was evidenced with level of education, previous AIDS diagnosis, CD4 cell nadir, current CD4 count, negative HIV RNA, NPZ-4 and NPZ-8 results.

DISCUSSION

Combination antiretroviral therapy (cART) had deeply changed the natural history of HIV-associated disorders with a continuous reduction of AIDS-events and AIDS-related death and a progressive increase in non-AIDS events and death by non-AIDS events[6]. Liver-related events (LRE) represent a consistent proportion of non-AIDS events, particularly in patients chronically co-infected with hepatitis viruses, and are a relevant cause of death, particularly in HIV-infected populations with high prevalence rates of HCV[5].

LRE are generated by a chronic hepatic necro-inflammatory damage and its repair, which causes multi-stage progressive fibrosis, leads to cirrhosis and its complications and to hepatocellular carcinoma (HCC). The main underlying causes are HBV or HCV co-infections, alcohol abuse and metabolic disorders with liver involvement[4]. The gold standard reference for determining hepatic

histology is liver biopsy. The stage of liver fibrosis can be determined by biopsy or by non-invasive methods, such as transient elastography or serum markers[6]. The FIB-4 index is one of these non-invasive serum fibrosis markers, which is determined using commonly available parameters such as transaminase levels, platelet counts and age. FIB-4 was initially developed and validated as a predictor of advanced fibrosis in HIV/HCV co-infected patients[6]. Later, It has been also validated in HCV mono-infected patients in whom it represents a robust predictor of histologic liver fibrosis stage[8] and subsequent liver events and death[8,9], although results are not consistent throughout studies[10].

In HIV/HCV co-infected patients, FIB-4 correlates with liver stiffness as measured by transient elastography and with liver fibrosis score determined by biopsy[12,13].

In settings where combination antiretroviral therapy (cART) is widely available, the burden of neurocognitive complications has shifted from HIV-Associated Dementia to milder forms of HIV-related neurocognitive impairment[1,14]. Although defined mild, these forms of impairment are associated with decreased ability to function in everyday life[15], making them a matter of concern.

Despite these remarkable improvements in immune health outcomes, HIV-associated neurocognitive disorders (HAND) remain a significant public health concern. Although neurocognitive impairments are not universal among HIV-infected persons, clinically obvious

signs and symptoms of at least mild neurologic disease are found in approximately 30% of persons with asymptomatic HIV infection and about 50% of individuals with AIDS[16]. While the incidence of the most severe form of HAND, HIV-associated dementia (HAD), has declined in the era of cART[17], the incidence and prevalence of milder forms of HAND have been relatively stable and may have even increased in individuals who are not immunosuppressed[18].

The detection decline in cognitive function may be particularly important clinically, as it suggests an active, potentially reversible process that requires further investigation and perhaps changes in management. Cognitive decline is typically identified with repeat neuropsychological testing[19].

We used a 8-test battery to evaluate neuropsychological performance in a cohort of HIV-mono infected patients with stable disease and good clinical conditions since more than 88% had an undetectable HIV RNA and median current CD4 count was above 790 cells/mm^3.

According to FIB-4 results, 48 (92.3%) patients had values <1.45 and 4 (7.7%) between 1.46 and 3.25 (26.2%), no patient had a value >3.25. Median FIB-4 value was 0.85 (IQR 0.70- 1.06). These data show that the level of hepatic fibrosis is low in HIV-infected patients receiving the modern antiretroviral therapy.

FIB-4 levels were significantly correlated with longer duration of known HIV infection (Rho=0.29, p<0.05) and longer cART exposure (Rho=0.36, p<0.05) whereas no correlation was evidenced with level of education, previous AIDS diagnosis, CD4 cell nadir, current CD4 count, negative HIV RNA, NPZ-4 and NPZ-8 results.

The role of ART in liver-related mortality in patients without chronic viral hepatitis is less well defined. In the Swiss HIV Cohort Study (SHCS), elevated alanine aminotransferase (ALT; reported as adverse events to antiretrovirals), was associated with a higher mortality, independent of chronic hepatitis virus coinfections[20]. In contrast, mortality was not increased in participants with chronic ALT elevation and without viral hepatitis in another SHCS analysis; however, the observation period was shorter and the patient number smaller[21]. Recently, new hepatic syndromes related to ART have emerged in HIV-infected persons. Noncirrhotic portal hypertension, a potentially life-threatening liver disease, has been linked to didanosine use[22,23]. Also, steatosis and steatohepatitis are common in HIV-positive persons with and without chronic viral hepatitis[24,25] and are associated with advanced liver fibrosis and cirrhosis[26]; ART as a risk factor has been discussed.

In the DAD study 22,910 participants without hepatitis virus coinfection for 114,478 person-years were in evaluated. There were 12 liver-related deaths (incidence, 0.10/1000 person-years); 7 due to severe alcohol use and 5 due to established ART-related toxicity. The rate of ART-related deaths in treatment-experienced persons was 0.04/1000 person-years (95% confidence interval, 0.01, 0.10). Therefore, the authors conclude that the incidence of liver-related deaths in HIV-infected persons without HCV or HBV coinfection is low. Liver-related mortality because of ART-related toxicity was rare[27].

Table 1. Demographic and clinical characteristics of the 52 patients enrolled.

Parameters	Values
Demographics data	
Age (years)	44 (38.5-50)
Gender	
Males	33 (63,4%)
Females	19 (36,6%)
Exposure Category	
Heterosexuals	29 (55.7%)
Previous AIDS diagnosis	12 (23.1%)
Duration of HIV infection (months)	168 (84-258)
CD4 count (cells/mm^3)	793 (616-1231.5)
CD4 nadir (cells/mm^3)	278.5 (161-385)
HIV RNA (log10 copies/ml) <40 cp/ml	46 (88.5%)

Data are expressed as median (interquartile range) or as number (percentage).

A recent study by Libertone et al in this large population of HIV-infected patients both with and without HCV infection, HAND was not associated with commonly used non-invasive liver fibrosis scores leading the authors to hypothesize a direct or indirect effect on cognitive function of the viruses, rather than the consequence of alterations residing outside the brain[27].

CONCLUSIONS

Most of our HIV mono-infected patients had a fully suppressed HIV RNA and FIB-4 values consistent with low levels of hepatic fibrosis. Higher FIB-4 results were significantly correlated with longer HIV infection and cART duration but not with neuro-cognitive performance, suggesting a dissociation between long-term hepatic toxicity and potential neuroprotective function of antiretrovirals.

CONFLICT OF INTERESTS:
The Authors declare that they have no conflict of interests.

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