

Fatty Liver Index is a Sensitive and Specific Marker of Non Alcoholic Fatty Liver Disease Measured by Transient Elastography in a Cohort of HIV Mono-Infected Patients

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Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is considered the hepatic manifestation of metabolic syndrome (MS) due to their frequent association, both linked to insulin resistance condition [1].

Nowadays NAFLD prevalence is rising in concert with the increasing burden of obesity and type 2 diabetes mellitus (DM), causing a substantial social problem in Western countries and, considering the lack of effective treatment, it is becoming one of the most common causes of chronic liver disease [2].

Among general populations NAFLD prevalence in Western countries varies from 14% to 31% while NASH prevalence ranges from 3–5% (>20% of NAFLD cases). It rises to 37% in morbid obesity [3].

In this setting early recognition and risk stratification of asymptomatic patients could lead to a significant challenge. Considering people who live with HIV, since the recognition of lipodystrophy, NAFLD cases have been described in HIV cases and now it is well known that is more common than in the general population and progress faster [4].

Indeed metabolic disorder have become one of the principal concern in the management of HIV patients: presence of metabolic syndrome, which promotes NAFLD, increased in HIV-infected patients from 19.4% in 2000–2001 to 41.6% in 2006–2007 [5,6].

Few data studied the prevalence of NAFLD among HIV mono-infected patients, which is reported higher than in general population and varies between 31%-37% [7].

Identification, staging and treatment of NAFLD is becoming one of the most important approaches to improve liver health among patients with HIV. The benchmark for NAFLD diagnosis is histological assessment of liver fat content through use of biopsy, however, it is costly, risky, and potentially painful [8].

Non-invasive diagnostic methods to assess liver damage include laboratory tests processed in diagnostic algorithms or mathematical models, such as NAFLD Fibrosis Score, AST to platelet ratio index (APRI) and The Fibrosis 4 score (FIB 4), Fatty liver index (FLI) and imaging evaluations [9-11].

NAFLD fibrosis score and FIB-4 scores are able to discriminate between presence or absence of advanced fibrosis in patients with NAFLD.

APRI score is a useful non-invasive marker of fibrosis and cirrhosis, FLI is a fatty liver markers with a strong association with metabolic syndrome presence.

Finally nowadays a consistent number of imagistic methods are available for diagnosing hepatosteatosis including ultrasound-based controlled attenuation parameter (CAP) and magnetic resonance imaging proton-density-fat-fraction (MRI-PDFF) [12,13].

Vibration-controlled transient elastography (VCTE), and shear wave elastography (SWE) are then useful to complete the evaluation with fibrosis quantification in patients with diagnosed NAFLD [14,15].

Accumulated data are present in literature concerning to Transient Elastography (TE) use with CAP measurements as a useful tool to evaluate NAFLD prevalence in asymptomatic HIV patients; although some studies included patients with HCV co-infection, a significant prevalence of hepatic steatosis (40-55% of cases) has been confirmed in HIV population [16]. Even though in this particular population noninvasive evaluation of steatosis, nonalcoholic steatohepatitis and fibrosis have been poorly assessed. The main aim of this study is to assess the performance of available non-invasive tools for screening and diagnosis of NAFLD in this particular setting of patients. Moreover, our work has also the purpose to identify the strongest NAFLD associated risk factor and then identify patients who required NAFLD assessment.

Methods

Study population

This is a single-center retrospective observational study carried out at the HIV Clinics of Infectious Disease Department at Policlinico San Matteo Hospital in Pavia – University of Pavia. We enrolled 252 consecutive patients referring to the Clinics for HIV infection follow up between 2014 and 2016. In this analysis we have excluded patients with other viral co-infection (HBV or HCV), history of alcoholic abuse (more than 4 drinks per day for men or more than 3 drinks per day for women) [17] or other causes of liver abnormalities. All participants were evaluated for height, weight, BMI, waist circumference and blood pressure.

Non invasive diagnostic tests definitions

Steatosis and fibrosis were retrospectively assessed by biochemical score and non-invasive diagnostic tests listed below used in general population: FLI, NAFLD fibrosis score, APRI and FIB4.

FLI is complex a mathematical algorithm based on triglyceride concentration, gamma-glutamyl transferase (GGT) level, body mass index (BMI), and waist circumference. It varies between 0 and 100. A FLI < 30 rules out NAFLD and a FLI \geq 60 rules in fatty liver [18,19].

NAFLD fibrosis score, based on age, Body Mass Index, AST/ALT ratio, platelets count, albumin amount and presence or absence of Impaired Fasting Glucose/diabetes diagnosis, is able to discriminate between the presence or the absence of advanced fibrosis in patients with NAFLD: with a low cutoff score (-1.455), advanced fibrosis could be excluded, and with the high cutoff score (0.676), presence of advanced fibrosis could be diagnosed [18].

AST to Platelet Ratio Index (APRI), combines AST and platelet values. For NAFLD patients APRI values lower or equal to 0.3 and lower or equal to 0.5 rule out respectively significant fibrosis and cirrhosis presence. Values higher to 1.5 rule in significant fibrosis [15,19].

FIB4, based on age, AST/ALT and platelet count is a useful tool to estimate the amount of scarring in the liver. In patients with NAFLD FIB4 score low than 1.30 stages fibrosis F0-F1, major than 2.67 stages fibrosis F3-F4. Among patients with suspected NAFLD the potential use should be restricted to evaluate the likelihood of having advanced or no fibrosis.

Laboratory tests Laboratory tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, fasting glucose, total cholesterol, high-density lipoprotein (HDL)-Cholesterol, low-density lipoprotein (LDL)-Cholesterol, triglycerides were assessed and used for those scores calculation jointly with physical examination including waist circumference and body mass index (BMI) determination.

Viral hepatitis panel with HBsAg and HCV-Ab detection has been used to exclude viral coinfection. Furthermore in all patients has been observed the CD4 cell count, viral load and therapeutic history, but those data have not been included in our analysis. In a sub group of 129 patients the Controlled Attenuation Parameter (CAP), implemented on Fibroscan device, has been performed.

Transient elastography and CAP Transient elastography (TE) with FibroScan is nowadays the most widely used noninvasive method in Europe for assessing the degree of liver fibrosis. It consists in the measurement of elastic shear wave speed propagating in the liver that relates directly to tissue stiffness; it is measured in KiloPascals [20].

During the liver stiffness assessment with TE, CAP algorithm calculate the attenuation of ultrasound signal and is expressed in dB/m. It provides a numerical value which correlates with the histological degree of steatosis. A cut-off value of 245 dB/m rules in liver steatosis with a very high specificity [21]. It's important to consider that for the validity of CAP in fatty liver diagnosis IQR must be ≥ 40 dB/m [22].

Statistical analysis

The primary end-point was the screening of our population living with HIV infection for the presence of liver steatosis, using biochemical score and non-invasive instrumental exams, validated in general population. We try to identify a correlation between biochemical scores each other and between scores and CAP. Secondary, in patients resulted positive for NAFLD, we investigated the presence of other components of Metabolic Syndrome and we try to find a correlation with NAFLD. Finally in patients positive for NAFLD a correlation between fibrosis score (APRI and FIB4) and Fibroscan has been tested.

Results

Baseline Demographic, Clinical, and Laboratory Characteristics The mean age of the study population ($n=252$) was 49 years (SD 12). 65% (164) were male, 35% (88) were female; 92% (233) reported being Caucasian, 5% (12) African American, 1.5% (3) Hispanic, and 1.5% (4) other.

Seventy one percent (108) of patients had dyslipidemia, defined as abnormalities in any of the lipid levels, particularly: 48% (120) had an elevated total cholesterol level >200 mg/dl, 34%(85) a LDL-Cholesterol >160 mg/dl, 15%(39) triglycerides >199 mg/dl, and 43%(109) a low HDL-Cholesterol <50 mg/dl.

The mean BMI of the group was 24.0 kg/m² (DS: 4) with 30% being overweight and 7% being obese. 17% of patients (43) had impaired fasting glucose (IFG) or diabetes mellitus diagnosis. 23% of patients (58 patients) were receiving anti-hypertensive medications and 14% of patients (35 patients) were receiving lipid-lowering medications.

Abnormal ALT and AST levels were noted in 17% (43) and 5.5% (14) of patients respectively. Of the elevated ALT and AST levels most were grade one, only few patients having grade two elevation and no patient with grade three or four elevation were observed.

Sub-analyzing the group of 128 patients that underwent Fibroscan with CAP we have divided the population into two groups: patients with positive CAP values, considered major or equal to 245 dB/m and suggesting NAFLD presence, versus patients with negative CAP values, defined as less than 245 dB/m, without NAFLD.

Evaluating some clinical, and laboratory characteristics we found significantly differences between the two groups that are summarized in the table 1. The average BMI of the groups was significantly different ranging from 22 in patients with negative CAP to 26 in patients with positive CAP values. Furthermore, as shown in table 1, metabolic panel presented some difference with triglyceride levels ranging from 111 mg/dl in patient with negative CAP value to 148 mg/dl in patients with positive CAP (Table 1).

Demographics		All patients	CAP <245	CAP >245
N. of patients		128	74 (57%)	54 (42%)
Age (years)		48 +/- 11	46 +/- 11	48 +/- 9
Male		83 (65%)	42 (57%)	41 (76%)
Race/ Ethnicity	With	115 (90%)	66 (89%)	50 (92,5%)
	African American	9 (7%)	6 (8%)	3 (5,5%)
	Hispanic	1 (1%)	0 (0%)	1 (1%)
	Other	3 (2%)	2 (3%)	1 (1%)
Body com- position	Body Mass Index (BMI)	24 +/- 4	22 +/- 2	26 +/-4
	<25 (Kg/m)	87 (68%)	63 (85%)	24 (44%)
	25-30 (Kg/m)	36 (28%)	11 (15%)	25 (46,5%)
	>30 (Kg/m)	5 (4%)	0 (0%)	5 (9%)
Metabolic panel	Waist circumference (cm)	89 +/- 13	85 +/- 13	94 +/- 12
	Fasting glucose >100mg/dl	19 (15%)	10 (13%)	9 (16%)
	Total Cholesterol > 200mg/dl	57 (44%)	31 (41%)	26 (48%)
	HDL <50 mg/dl	52 (40%)	28 (38%)	26 (48%)
	LDL > 130mg/dl	9 (7%)	6 (8%)	18 (33%)
	Triglycerides >150mg/dl	37 (29%)	15 (20%)	22 (40%)

Metabolic panel (Average)	Fasting glucose (mg/dl)	93 +/- 19	92 +/- 22	94 +/- 19
	Total Cholesterol (mg/dl)	194 +/- 39	191 +/- 40	197 +/- 37
	HDL (mg/dl)	55 +/- 16	56 +/- 16	52 +/- 14
	LDL (mg/dl)	114 +/- 32	112 +/- 32	115 +/- 29
	Triglycerides (mg/dl)	127 +/- 68	111 +/- 36	148 +/- 76
Metabolic syndrome	DM	19 (15%)	10 (13%)	9 (16%)
	Hypertension	18 (14%)	6 (8%)	12 (22%)
	on lipid-lowering drugs	13 (10%)	5 (7%)	8 (4%)
Liver function test	ALT > 34 IU/L	23 (18%)	10 (13,5%)	13 (24%)
	AST > 39 IU/L	10 (8%)	4 (5%)	6 (11%)
Scores	FLI (> 60)	28 (22%)	6 (8%)	22 (41%)
	NAFLD (> 0,675)	4 (3%)	3 (4%)	1 (1,8%)
	APRI (> 1,5)	1 (0,8%)	0 (0%)	1 (2%)
	FIB4 (> 2,67)	3 (2%)	1 (1,3%)	2 (4%)

Table 1: Demographic, Clinical and Laboratory Characteristics associated with NAFLD stratify by CAPDemographics All patients CAP <245 CAP >245.

Prevalence of NAFLD

Among the whole group of 252 patients we identified 60 (24%) with positive Fatty Liver Index (>60) and 7 (3%) with positive NAFLD score (>0,675).

128 patients underwent to Fibroscan with Controlled Attenuation Parameter (CAP), 54 of them (42%) resulted positive for NAFLD presence, considering 245 dB/m as positive cut-off; 22% of patients (28/128) showed positive values of Fatty Liver Index with a cut-off of 60; 41% (22/54) of patients among the positive CAP group had also a positive FLI score. On the other hand , only 8% of patients (6/74) in the group with CAP < 245 dB/m presented a positive FLI score.

CAP < 245 dB/m presented a positive FLI score. On statistical analysis a significant correlation between FLI and CAP has been founded: considering the group of patients with positive FLI score we found higher FLI levels when also CAP was positive and a lower level when CAP was negative (Figure 1-2).

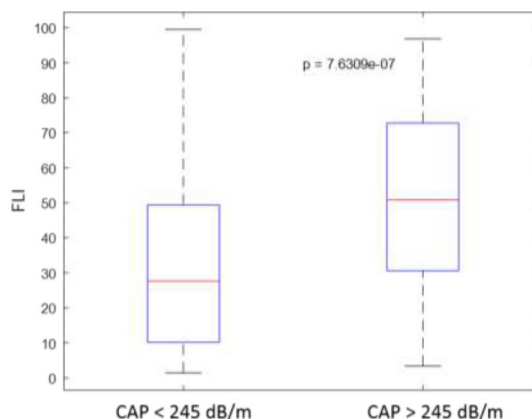


Figure 1: Relationship between FLI and CAP. Patients with positive CAP showed higher levels of FLI, patients with negative CAP presented lower levels of FLI.

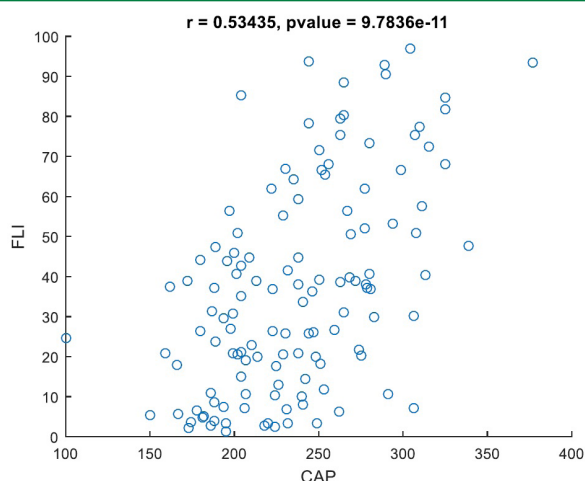


Figure 2: Distribution of Fatty Liver Index (FLI) reported to Controlled Attenuation Parameter (CAP) values.

To evaluate FLI performance in this group of HIV patients screened for NAFLD with Controlled Attenuation Parameter we performed a Receiver-Operating Characteristics curve (ROC). The AUROC of FLI for CAP ≥ 245 was 0.758.

Considering a cut-off value of 47.7, the sensitivity and specificity predictive for steatosis presence were optimal with 0.54 and 0.87 values respectively. Whereas accepted value of significant FLI in steatosis identification is 60, decrease the cut-off in this population could point out a significant portion of people at risk for NAFLD otherwise not identifiable (Figure 3).

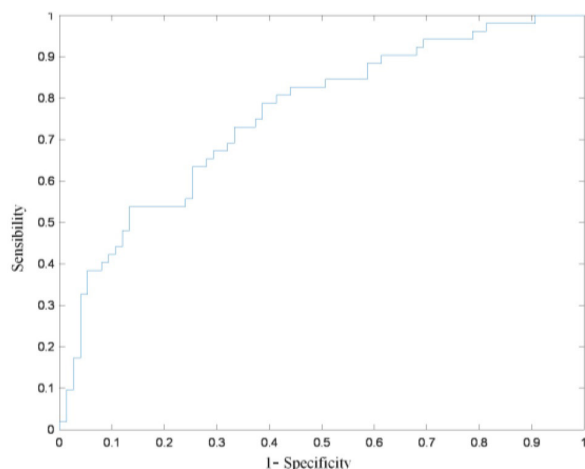


Figure 3: The AUROC of Fatty Liver Index for CAP = 245 dB/m is 0.758.

Focusing now our attention on NAFLD score, whereas we found a correlation between FLI and CAP, on statistical analysis there is not any significant correlation between NAFLD score and CAP ($p=0.02$). NAFLD score was positive in seven patients (3%) among the whole group of 252 patients and in four patients (3%) among the sub-group screened with CAP.

Considering the sub-group that underwent to CAP we have not found any significant correlation between NAFLD score positivity or values and CAP results (Figure 4).

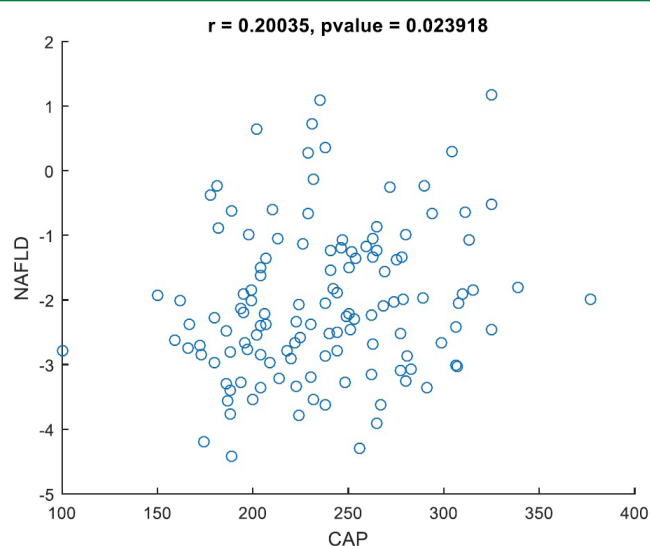


Figure 4: Distribution of NAFLD score reported to Controlled Attenuation Parameter (CAP) values.

Evaluating fibrosis scores APRI and FIB4 we found a positivity in one (0.4%) and four (1.5%) patients respectively in the whole group of 252 patients, considering values of >1.5 for APRI and >2.67 for FIB4 as positive cut-off. Among the group with positive CAP values only one patient (2%) had a positive APRI and only two patients (4%) had a positive FIB4.

On statistical analysis, as expected, we found a strong association between APRI and FIB4 ($p<0.01$) and between the scores and Fibroscan values ($p<0.01$) whereas there is not significant correlation between those scores and CAP. Furthermore on our dataset there is no significant correlation between CAP and Fibroscan ($p=0.8$).

Moreover APRI and FIB4 are correlate, as expected, with NAFLD score: NAFLD score values increase with the increasing of APRI and FIB4 (Figure 5-6).

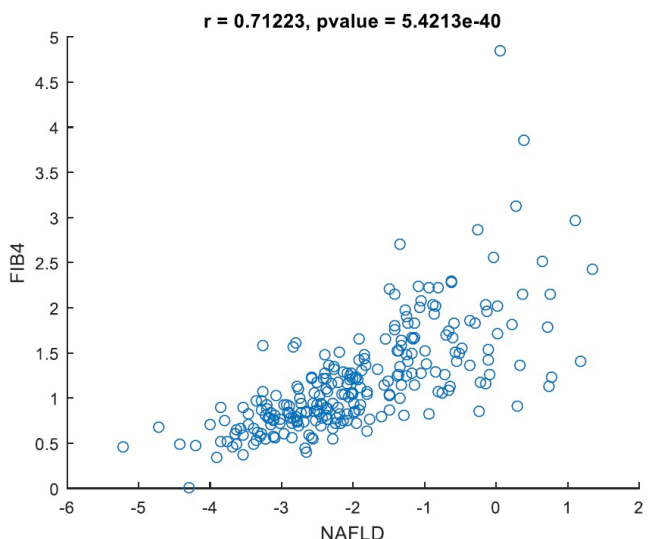


Figure 5: Distribution of FIB4 score reported to NAFLD score values.

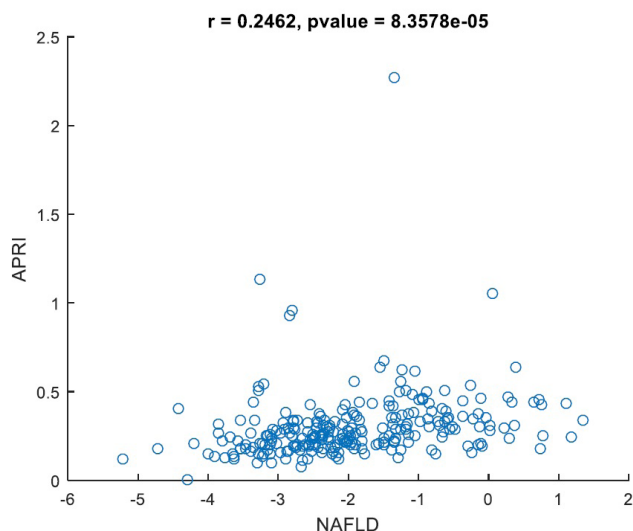


Figure 6: Distribution of APRI score reported to NAFLD score values.

Risk Factors Associated with NAFLD in HIV patients

NAFLD has been categorized into two group, present or absent, in relation with CAP values. Available variables including BMI, triglycerides, total cholesterol, LDL cholesterol levels, HDL?? AST, ALT values, presence or absence of impaired fasting glucose/ diabetes mellitus diagnosis and hypertension, age and sex have been included in multivariate analyses.

Because waist circumference was highly correlated with BMI we excluded it from multivariate regression model. Multivariate model showed that higher BMI (OR 1.38 $p < 0.001$) and triglycerides levels ($p = 0.04$) were significantly associated with NAFLD.

Hypertension and impaired fasting glucose or diabetes diagnosis, the other essential correlates of metabolic syndrome, did not reach statistical significance in multivariate model, probably due to the small simple size (Figure 7).

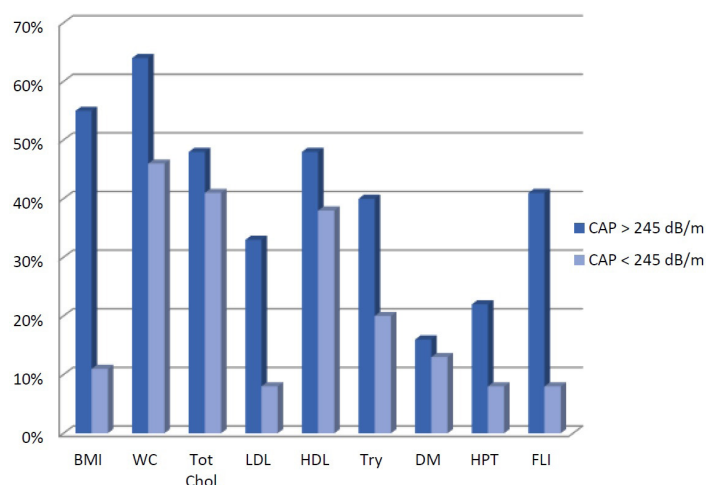


Figure 7: Risk Factors Associated with NAFLD in HIV patients stratify by CAP values BMI> 25 Waist circumference 94 cm in men and 80 cm in women, Total Cholesterol 200 mg/dl, Cholesterol LDL> 130 md/dl, Cholesterol HDL< 50 mg/dl, Tryglicerides 150 mg/dl.

Discussion

NAFLD, evaluated by Controlled Attenuation Parameter implemented on the Fibroscan device, is common among HIV patients of our cohort occurring with a prevalence of 42%. Increased BMI and elevated triglycerides levels were significantly associated with NAFLD. In our observation FLI is a well performing score significantly correlated with NAFLD presence

Identifying patients at risk of NAFLD might have important clinical implications that involves both the evolution of liver diseases and the cardiovascular risk morbidity and mortality; NAFLD presence should be considered a marker of systemic metabolic disorder and suggests the screening for other cardiovascular risk factors coexistence.

On this basis NAFLD screening and early identification may have a significant impact on HIV patients management. Fatty Liver Index is a simple, rapid and successful instrument that allow to identify people at risk [23]. Among our cohort FLI was significant for suspected steatosis at a cut-off value lower than in general population suggesting that a greater portion of patient needs to be screened.

The strongest factor associated with NAFLD in our study was an increased BMI. This is consistent with other studies of HIV mono-infection and HIV-HCV co-infection where BMI was significantly associated with steatosis [24]. Waist circumference and BMI may be the best predictor of obesity-related health risk because they are tightly correlate with visceral fat accumulation and then with insulin resistance development.

High triglycerides levels were also associated with NAFLD among our HIV positive cohort. This finding is consistent with available knowledges about the pathogenesis of NAFLD that involves alteration of synthesis and storage of triglycerides in hepatocytes [24,25].

Although few data are available about people living with HIV, different studies analyzing HIV-HCV co-infected and general population confirmed that elevated triglycerides levels and low HDL levels are independent factors for steatosis [25].

Focusing on our population, we know that these lipid alterations are common among HIV-positive individuals, likely due to viral influences as well as antiretroviral medication effects or life style in general [26].

Given these data, an effort to maintain triglycerides and HDL levels within a normal range might be a determinant key factor in the prevention of NAFLD and its consequences.

Although besides liver enzyme abnormalities are commonly observed among HIV patients, their sensitivity and specificity for detecting NAFLD are low [27].

Generally the elevation of transaminases caused by NAFLD is

mild to moderate with a AST/ALT ratio less than 1, with most of patients (up to 79%) with normal liver test [28]. Lack of strong association between transaminases levels and NAFLD presence emerged also in our observation.

Therefore, thought liver tests alone are not useful to make diagnosis of NAFLD, their persistent alteration, particularly in patients with classical metabolic phenotype, suggest NAFLD assessment. Indeed latest EACS (European AIDS Clinical Society) Guidelines recommend assessment for liver disease severity and NAFLD presence in all HIV patients with unexplained liver test abnormalities [29].

Relationship between NAFLD and advanced fibrosis was not found at score/non-invasive tools comparison.

This study has some limitations. First it is a retrospective cross-sectional study unable to define the dynamic process underlying the development of both steatosis and fibrosis in HIV patients. Despite our data are encouraging, steatosis detection using CAP is not yet an approved gold standard technique. Then we have not considered the newest conclusion of CAP study attesting the new cut-off for steatosis at 248 dB/m and stratifying S1-S2-S3 at 248-268-280 cut-off values respectively [30]. Then in our analysis we haven't considered the possible interaction with variables such as different specific antiretroviral therapy regimens or with HIV infection duration, HIV viral load or CD4 cells count.

On the other hand, our observation point out that NAFLD is common among HIV patients and may be a reminder for the clinician to focus on cardiovascular comorbidity and to an increased risk of advanced fibrosis or cirrhosis. Screening or early identification of NAFLD is a key point in patient management since so far there are not effective therapeutic strategies.

Contextualize NAFLD in the broad spectrum of metabolic systemic dysfunction may improve the clinical approach to the patient with possibility to stratify and prevent CV risk and reduce the impact of non-HIV related mortality. Finally, scores and non-invasive diagnostic techniques, CAP particularly, are promising tools requiring further study to obtain a validation also among people living with HIV and optimize the clinical practice use. Among them Fatty Liver Index is the most useful to identify people at risk of NAFLD which deserve to be investigated and successively examined with CAP.

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