Prevalence and severity of Nonalcoholic Fatty Liver Disease by Transient Elastography with Controlled Attenuation Parameter: risk factors in unselected HIV mono-infected population

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Background

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of liver injury in Western countries. The risk to develop NAFLD is higher for HIV-infected patients. In non-HIV patients, prevalence of and the risk factors related to NAFLD are well documented, together with complications. By contrast, there are limited data on NAFLD in the HIV-infected population[1].

Material And Methods

Between January and June 2018, 643 HIV-infected patients in active follow-up underwent transient elastography (TE) examination with controlled attenuation parameter (CAP). We prospectively investigated prevalence and predictors of NAFLD and liver fibrosis by TE and CAP in unselected HIV-infected adults without significant alcohol intake (< 20g/die), viral hepatitis coinfection and other causes of liver disease. We excluded from the sample all failed TE examination and unreliable measurements (Figure 1). NAFLD and severe NAFLD were defined as CAP at least 248 dB/m and 285 dB/m, respectively. Significant liver fibrosis and cirrhosis were defined as TE measurement at least 7.1 and 13 kPa, respectively [2,3]. Predictors of NAFLD and significant liver fibrosis in patients with steatosis were determined using logistic regression analysis, including covariates that were statistically significant in the univariable analysis. Statistical analyses were performed using IDE RStudio (Vers 0.98.945).

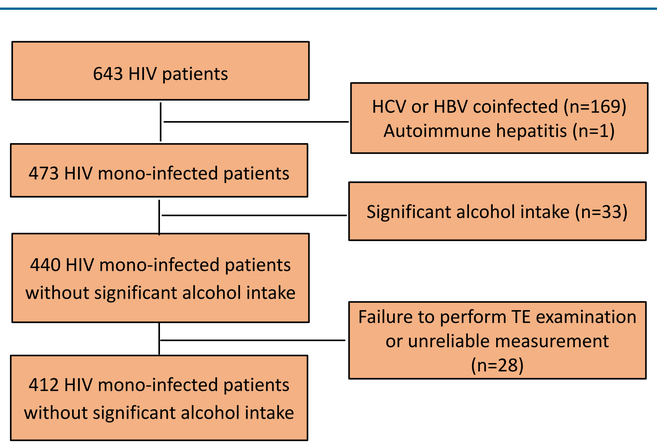

Figure 1. Flow chart displaying the selection of study participants. Of 643 consecutive HIV patients who had a transient elastography examination done at the University Hospital of Palermo (Italy) and had available laboratory data, 170 were excluded because of coinfection with HCV or HBV and other liver disease, 33 because of significant alcohol intake, 28 because of failure to perform transient elastography examination or unreliable measurement (defined as < 10 validates measures and an interquartile range > 30%).
HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; TE, transient elastography.

Results

A total of 412 consecutive HIV mono-infected patients (mean age 47 years, 72% men, mean CD4+ cell count 700 cells/µL, 98% on antiretrovirals) were included. Prevalence of NAFLD and severe NAFLD in the cohort is 42.7% and 25%, respectively, while prevalence of significant liver fibrosis and cirrhosis is 14.3% and 2%, respectively. Restricting the sample to steatosic population, prevalence of fibrosis is 9.7%. The results of univariable analyses are shown in Table 1.

After adjustment, NAFLD is associated with BMI (Body Mass Index), sex, elevated ALT, triglycerides and previous exposure to old NRTI (AZT, ddI, d4T). As expected, BMI is a predictor of significant liver fibrosis in steatosic patients. Conversely, previous use of more recent protease inhibitors (ATV, DRV) seems to protect against liver fibrosis in patients with NAFLD (Table 2 and 3).

Conclusions

In our cohort of HIV mono-infected patients, NAFLD is frequently observed and a significant proportion of patients has fibrosis. Metabolic conditions and elevated ALT are main predictors. The protective value of more recent protease inhibitors (ATV and DRV) versus evolution in fibrosis is interesting although controversial, therefore further investigation is required. Diagnostic assessment with TE examination allows early recognition of NAFLD in HIV population, and consequently, life-style modifications to prevent complications and improve liver damage.

Table 1. Demographic, clinical, biochemical, virological and pharmacological characteristics of the study population (n=412) and univariable analyses by outcome status, that is presence of nonalcoholic fatty liver disease or significant liver fibrosis in patients with NAFLD.

Variable		CAP ≥ 248 (n = 176)	CAP < 248 (n=236)	CAP ≥ 248 TE ≥ 7.1 (n=40)	CAP ≥ 248 TE < 7.1 (n=136)
Male sex (%)		139 (79)**	156 (66)	31 (78)	108 (79)
Ethnicity (%)					
	White	160 (91)	201 (85)	37 (92)	123 (90)
	Black non Hispanic	16 (9)	33 (14)	3 (8)	13 (10)
	Hispanic	0	1 (0,5)	0	0
	Other	0	1 (0,5)	0	0
Risk factor for HIV infection (%)					
	Heterosexual	88 (50)	126 (54)	24 (60)	64 (47)
	MSM	80 (45)	100 (42)	14 (35)	66 (49)
	IVU	8 (5)	5 (2)	2 (5)	6 (4)
	Other/Unkown	0	5 (2)	0	0
BMI		26 (20-38)**	23 (16-34)	29 (21-38)**	25 (20-37)
Smoking (%)		76 (43)	114 (48)	12 (30)	64 (47)
Cannabis (%)		3 (2)	4 (2)	0 (0)	3 (2)
Hypertension (%)		57 (32)	39 (17)	16 (40)	41 (30)
Diabetes (%)		12 (7)	13 (6)	1 (2)	11 (8)
Cardiovascular disease (%)		22 (13)	18 (8)	5 (13)	17 (13)
Dyslipidaemia (%)		88 (50)	64 (27)	17 (43)	71 (52)
Time since HIV diagnosis (years)		12 (0-30)*	8 (0-33)	9 (1-29)	12 (0-30)
HIV viral load < 20 cp/ml (%)		168 (95)*	213 (90)	38 (95)	130 (96)
History of CD4 cell count < 200/mmc (%)		86 (49)	87 (37)	18 (45)	68 (50)
CD4 cell count		703 (60-1641)	666 (16-1882)	760 (60-1157)	697 (139-1647)
On ART (%)		174 (99)	224 (95)	40 (100)	135 (99)
Time in ART (years)		12 (0-29)	7 (0-32)	11 (1-29)	12 (0-28)
ART ever prescribed (%)					
	old PI	69 (39)*	60 (25)	10 (25)*	59 (43)
	new PI	104 (59)	121 (51)	17 (43)*	87 (64)
	EFV/NVP	70 (40)	80 (34)	19 (48)	51 (38)
	RVP/ETV	39 (22)	46 (19)	12 (30)	27 (20)
	TDF/ABC/FTC	173 (98)	226 (96)	39 (98)	134 (99)
	AZT/ddI/d4t	75 (43)*	63 (27)	17 (43)	58 (43)
	INI	105 (60)	142 (60)	26 (65)	79 (58)
ART cumulative exposure (days)					
	old PI	2920(120-8030)	2920 (0-9490)	2372 (0-7300)	2920 (0-8030)
	new PI	1825 (120-5110)	1825 (0-6570)	2190 (0-5110)	1825 (0-4745)
	EFV/NVP	2920 (365-6570)	2190 (0-8030)	2920 (0-5840)	2190 (0-6570)
	RVP/ETV	1095 (30-3650)	1095 (0-3650)	1460 (0-3285)	1095 (0-3650)
	TDF/ABC/FTC	2555 (30-7300)	1825 (0-7300)	2555 (0-6935)	2555 (0-7300)
	AZT/ddI/d4t	2920 (120-7300)	3285 (0-7300)	2555 (0-6570)	3102 (0-7300)
	INI	880 (30-3650)	730 (0-5110)	1095 (0-3650)	730 (0-3650)
Current ART used (%)					
	old PI	0 (0)	2 (1)	0 (0)	0 (0)
	new PI	74 (42)	83 (35)	13 (33)	61 (45)
	EFV/NVP	10 (6)	13 (6)	3 (8)	7 (5)
	RVP/ETV	31 (18)	37 (16)	8 (20)	23 (17)
	TDF/ABC/FTC	142 (81)	197 (83)	34(85)	108 (79)
	AZT/ddI/d4t	2 (1)	2 (1)	1 (2)	1 (1)
	INI	104 (59)	140 (59)	26 (65)	78 (57)
ALT (IU/L)		23 (7-75)	19 (6-106)	23 (9-75)	22 (7-71)
AST (IU/L)		21 (10-66)	19 (6-106)	21 (11-42)	21 (10-66)
ALT > ULN (%)		65 (37)*	57 (24)	15 (38)	50 (37)
Total cholesterol (mg/dl)		181 (101-413)*	174 (81-367)	185 (127-247)	181 (101-413)
Triglycerides (mg/dl)		121 (44-660)**	97 (36-454)	121 (44-660)	120 (49-570)
Tryglycerides ≥ 150 (%)		67 (38)	59 (25)	15 (38)	52 (38)
LDL-cholesterol (mg/dl)		110 (33-272)*	101 (21-262)	103 (42-177)	110 (33-272)
HDL-cholesterol (mg/dl)		43 (20-114)	49 (19-120)	44 (20-81)	43 (25-114)
HDL ≤ LLN (%)		49 (28)	83 (35)	20 (50)	59 (43)
Fasting glucose (mg/dl)		89 (60-194)	86 (61-237)	89 (66-129)	89 (60-194)
Platelet count (10^9/L)		232 (54-486)	242 (58-600)	258 (158-374)	230 (54-486)
APRI		0.002 (0.001-0.1)	0.002 (0.001-0.017)	0.002 (0.001-0.006)	0.002 (0.001-0.01)
FIB-4		0.868 (0.255-2.988)	0.811 (0.199-4.680)	0.807 (0.337-1.507)	0.883 (0.255-2.988)
eGFR ml/min sec. CKD EPI		92 (17-141)	98 (6-154)	89 (60-132)	94 (17-141)

Continuous variables are expressed as median (IQR) and categorical variables as numbers (%). The P value refers to t test o χ^2 test between patients with the outcome (nonalcoholic fatty liver disease or significant liver fibrosis in patients with NAFLD) and the correspondent counterpart of patients without outcome.
ART, antiretroviral therapy; PI, protease inhibitor; EFV, efavirenz; NVP, nevirapine; RPV, rilpivirine; ETV, etravirine; TDF, tenofovir disoproxil fumarate; ABC, abacavir; FTC, emtricitabine; AZT, azitotimidine; ddI, didanosine; d4t, stavudine; INI, integrase inhibitor; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; LLN, lower limit of normal; APRI, AST to Platelet Ratio Index; FIB-4, fibrosis-4 score; IVDU, intravenous drug users; eGFR, estimated glomerular filtration rate; CAP, controlled attenuation parameter; TE, transient elastography. *$P < 0.05$ **$P < 0.01$

Table 2. Multivariable analysis of predictors of nonalcoholic fatty liver disease (controlled attenuation parameter ≥248 dB/m).

Variable	aOR (95% CI)	p-value
Age**	1.02 (0.99 - 1.04)	0.16
Gender (Male sex)*	**2.24 (1.28 - 3.97)**	**0.004**
Duration of HIV infection (per year)**	0.96 (0.92 - 1.02)	0.17
Viral load < 20 cpm *	0.45 (0.17 - 1.13)	0.10
BMI**	**1.23 (1.15 - 1.32)**	**< 0.001**
ALT> ULN (yes vs. no)*	**1.84 (1.12 - 3.03)**	**0.02**
Total cholesterol **	0.99 (0.97 - 1.00)	0.10
Triglycerides **	**1.01 (1.00 - 1.01)**	**0.006**
Low Density Lipoprotein **	1.02 (0.99 - 1.04)	0.05
TDF/ABC/FTC ever used (yes vs. no)*	2.67 (0.65 - 14.29)	0.20
AZT/other old NRTI ever used (yes vs. no)*	**2.44 (1.08 - 5.61)**	**0.03**
Old PI ever used (yes vs. no)*	1.93 (0.96 - 3.94)	0.06

Table 3. Multivariable analysis of predictors of significant liver fibrosis (transient elastography measurement ≥ 7.1 kPa) in patients with NAFLD (controlled attenuation parameter ≥ 248 dB/m).

Variable	aOR (95% CI)	p-value
Gender (Male sex)*	0.91 (0.34-2.59)	0.85
BMI**	**1.22 (1.10-1.36)**	**< 0.001**
Platelet count**	1.00 (0.99-1.01)	0.42
Old PI ever used (yes vs.no)*	0.65 (0.25-1.59)	0.35
New PI ever used (yes vs. no)*	**0.41 (0.17-0.95)**	**0.03**

Adjusted odds ratio and 95% CIs are shown for each variable analysed in multivariate logistic regression models. P-value is considered significant when less than 0.05. * categorical variable; ** continuous variable.

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