Risk factors for liver fibrosis progression in HIV: a multi-center longitudinal study

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Background

- People with HIV (PWH) are at high risk for metabolic dysfunction-associated fatty liver disease (MAFLD).
- Liver fibrosis (LF) is the most significant predictor of liver disease progression and mortality.
- We aimed to investigate the effect of MAFLD and antiretroviral exposure on LF progression in PWH.

Methods

- This was a longitudinal study of three large prospective cohorts of PWH in Italy, Germany and Canada.
- Patients with at least two transient elastography with controlled attenuation parameters (CAP) exams were included.
- LF progression was defined as development of significant LF (defined as liver stiffness ≥8 kPa), or transition to cirrhosis (defined as liver stiffness ≥13 kPa for those with liver stiffness ≥8 but < 13 kPa at baseline).
- MAFLD was defined according to Eslam criteria: presence of hepatic steatosis (CAP≥248 dB/m), plus any among type 2 diabetes, overweight (BMI>25 Kg/m^2) or two other metabolic abnormalities.

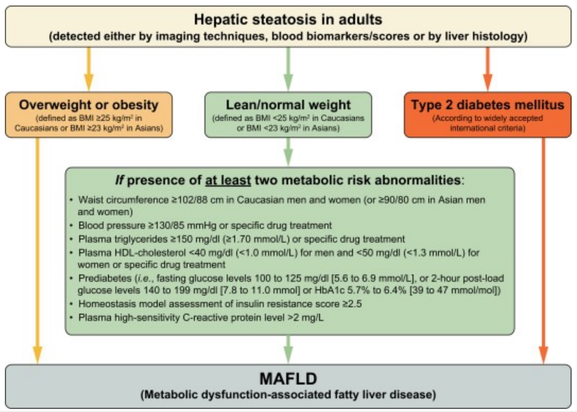

Figure 1. *MAFLD criteria according to Eslam M. JHepatol.2020;73(1):202-209].*

- Other longitudinal predictors included co-infection with HBV or HCV, weight gain (WG), defined as a 5% BMI increase in two consecutive visits, and current exposure to ART classes.
- A multi-state Markov model was used to describe the process in which PWH moved through the next LF state.
- Cox regression model was used to identify predictors for LF progression event.

Liver fibrosis progression occurs in a significant proportion of PWH.

Metabolic associated fatty liver disease, BMI and weight gain were associated with higher risk of liver fibrosis progression.

Men had lower risk of liver fibrosis regression.

Virus hepatitis B and C were not associated with liver fibrosis progression, probably due to adequate management of chronic HBV infection and successful treatment of HCV.

Results and discussion

- A total of 1183 PWH were included (median age 52.9 years, 77% males, median duration since HIV diagnosis 18 years). Prevalence of MAFLD was 46.8%. Coinfections with HBV and HCV were present in 3.6% and 21.9%, respectively.
- At baseline, liver stiffness was <8 kPa in 85.6%, 8-12.9 kPa in 8.6%, and ≥13 kPa in 5.7% of PWH.

Table 1. *Demographic, anthropometric and HIV characteristics of liver fibrosis progressors and non-progressors.*

	No progression (N=1062, 89,8%)	Progression (N=121, 10,2%)	p
Male sex, N (%)	816 (76.8%)	101 (83.5%)	0.10
Age, years, median (Q1, Q3)	53.0 (46.6-58.2)	51.7 (44.6-58.8)	0.77
BMI, kg/m2, median (Q1, Q3)	24.1 (21.9-26.2)	26.0 (23.2-29.0)	**<0.001**
BMI gain, >5%, N (%)	166 (22.8%)	19 (29.7%)	0.21
Current CD4 cell count, c/microL, median (Q1, Q3)	626 (457-818)	601 (384-798)	0.45
Nadir CD4 cell count, c/microL, median (Q1, Q3)	200 (96-311)	176 (95-305)	0.65
Years since HIV diagnosis, years, median (Q1, Q3)	18.4 (9.1-27.0)	15 (8.0-25.2)	**0.04**
MAFLD, N (%)	261 (46.4%)	46 (65.7%)	**0.002**
HBV, N (%)	32 (3.0%)	10 (8.3%)	**0.003**
HCV, N (%)	225 (21.2%)	32 (24.8%)	0.36

- During a median follow-up period of 2.5 years, a minimum of two and maximum of six yearly LF assessments were performed.
- The incidence rate of LF progression was 3.4 per 100 persons-year.

Table 2. *Markov model describes transition (progression or regression) of liver fibrosis (odds ratios with confidence intervals).*

	No fibrosis - fibrosis (progression)	Fibrosis – no fibrosis (regression)
Age (>50 vs. <50)	0.989 (0.947, 1.033)	0.988 (0.954, 1.024)
Males (vs. females)	0.871 (0.363, 2.089)	**0.321 (0.137, 0.754)**
BMI (>25 vs. <25)	**1.122 (1.043, 1.207)**	1.001 (0.902, 1.111)
BMI gain (>5% vs. <5%)	**3.107 (1.588, 6.078)**	**0.285 (0.097, 0.838)**
Years since HIV diagnosis (10-20 vs. <10)	1.085 (0.4, 2.947)	1.19 (0.425, 3.334)
Years since HIV diagnosis (>20 vs. <10)	1.142 (0.399, 3.266)	0.925 (0.325, 2.638)
Nadir CD4 cell count (<200 vs. >200)	1.033 (0.526, 2.029)	0.78 (0.351, 1.737)
HBV (yes vs. no)	1.79 (0.517, 6.196)	0.304 (0.037, 2.514)
HCV (yes vs. no)	1.647 (0.789, 3.435)	0.63 (0.286, 1.385)
Current exposure to INSTI	0.613 (0.259, 1.45)	0.73 (0.337, 1.584)
Current exposure to PI	0.849 (0.35, 2.059)	1.168 (0.546, 2.496)
Current exposure to NNRTI	0.406 (0.148, 1.111)	0.991 (0.451, 2.175)
Current exposure to TAF	1.114 (0.549, 2.259)	0.96 (0.43, 2.144)

Table 3. *MAFLD was not included in the multi-state Markov model (Table 2) due to a significant proportion of missing data on MAFLD across visits, therefore a Cox regression analysis was preformed.*

	Cox regression analysis of the liver fibrosis progression		
Predictors	Hazard ratio	CI	p
Current exposure to INSTI	1.47	0.61 – 3.52	0.389
Current exposure to TAF	0.85	0.39 – 1.87	0.683
Current exposure to NNRTI	0.83	0.32 – 2.18	0.704
Current exposure to PI	1.53	0.64 – 3.63	0.340
Male sex	1.08	0.43 – 2.71	0.863
Age at baseline	0.99	0.95 – 1.04	0.690
Nadir CD4 <200	0.56	0.27 – 1.17	0.120
Years since HIV diagnosis	1.05	1.00 – 1.10	0.064
Chronic hepatitis B virus infection	2.08	0.56 – 7.69	0.272
Chronic hepatitis C virus infection	1.08	0.45 – 2.57	0.868
MAFLD	**2.50**	**1.06 – 5.89**	**0.036**
BMI gain > 5%	**2.64**	**1.32 – 5.26**	**0.006**

Conclusion

- LF progression occurs in a significant proportion of PWH, higher than reported in literature for the general population.
- Its main drivers include metabolic health variables, while ART exposure does not seem to impact LF progression.
- PWH should be routinely screened for liver fibrosis, regardless of viral hepatitis co-infection.

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