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Risk factors associated with NAFLD in people living with HIV

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Introduction

Non alcoholic fatty liver disease (NAFLD) has become the main cause of chronic liver disease in high and middle-income countries. Its prevalence seems to be higher in people living with HIV (PWH)[1] due to known metabolic factors as well as triggers due to chronic HIV infection, including a controversial role of combination-antiretroviral therapy (cART)[2].

Study Design

We are conducting a **multicentric prospective cohort study** aiming to define **risk factors associated with NAFLD and progression of steatosis in PWH** over a 4 years period of time.

We enrolled patients ≥ 18 years old (yo) with steatosis documented by ultrasound (US). We included patients with BMI < 40 kg/m² and without secondary causes of hepatic steatosis (HCV-HBV coinfection, daily alcohol intake > 20 g in men and > 10 g in women).

Methods

During follow up patients were evaluated with clinical examination comprehensive of blood tests and ultrasound every 12 months while elastography (using Fibroscan) was performed every 24 months.

- Patients general data included age, sex and clinical assessment of metabolic risk factors (BMI, waist circumference, blood pressure, lipidic profile, presence of diabetes)
- We collected patients' data about current and previous cART, both qualitative (yes/no) and quantitative exposure (months), and immuno-virological status
- Fibroscan was performed to evaluate presence and severity of steatosis according to CAP values: **no steatosis (S0; CAP < 248 dB/m), mild steatosis (S1; 248 dB/m ≤ CAP < 268 dB/m), moderate to severe steatosis (S2-S3; CAP ≥ 268 dB/m)**
- FIB-4 index, APRI score, FAST-score and liver stiffness measured by Fibroscan were calculated to assess liver fibrosis
- To evaluate risk factors, patients were stratified into groups based on CAP measures as follows: **S0 vs S1-S3; S0-S1 vs S2-S3**
- Groups were compared using a logistic regression, to evaluate the strength of association with patients' characteristics at study entry (odds ratios, OR, and 95% confidence interval, CI). Multivariate equation included the factors statistically significant at the univariate analysis.

Results

Patient cohort

We enrolled **101 PWH**, here we present data collected as of March 2023.
The mean age of our cohort was 55.2 (SD ±12) yo, most of them were males [87 (86.1%)]. The mean BMI was 28.1 (SD ± 4.2) kg/m² and the majority had metabolic syndrome [51 out of 73 people evaluated (69.9%)], 25 PWH had diabetes (24.8 %). The median CD4+ cell count was 768 [Interquartile range (IQR) 562-1013] cell/mm3, a detectable HIV-RNA viral load was only found in 5 (5%) patients and the median duration of infection was 12.6 (IQR 8-24.2) years. Considering current cART, 51 patients had a TAF-based regimen (50.5%) and 10 patients had a TDF-based one (9.9%), 69 patients had an INSTI-containing regimen (68.3%), NNRTI [31 (30.7%)], PI [9 (8.9%)].

Fibroscan was performed: **72 patients (71.3%) had CAP≥ 248 dB/m, 63 (62.4%) had CAP ≥ 268 dB/m**.
Characteristic of patients according to the presence and grading of NAFLD are shown in table 1.

Table 1. Patients' characteristics according to CAP (dB/m)

	S0 CAP > 248	S1-S3 CAP ≥ 248	S0-S1 CAP < 268	S2-S3 CAP ≥ 268
Age	52.5 ± 11.6	56.3 ± 12.1	53.7 ± 11.6	56.1 ±12.3
Gender	26 (89.7%)	61 (84.7%)	34 (89.5%)	53 (84.1%)
BMI kg/m-2	**26.5 ± 4.6**	**28.8 ± 3.9**	**27.2 ± 4.4**	**28.8 ± 4.0**
Metabolic Syndrome	14 (63.6%)	37 (72.6%)	20 (66.7%)	31 (72.1%)
Diabetes	**3 (10.3%)**	**22 (30.6%)**	**5 (13.2%)**	**20 (31.8%)**
Cd4 cell count, cell/mm3	704 (528-917)	794 (581-1019)	708 (528-917)	796 (566-1025)
Detectable HIV-RNA	1 (3.4%)	4 (5.6%)	1 (2.6%)	4 (6.4%)
Exposure to TAF	**22 (75.9%)**	**38 (52.8%)**	**29 (76.3%)**	**31 (49.2%)**
Exposure to DTG	11 (37.9%)	40 (55.6%)	**12 (31.6%)**	**39 (61.9%)**
Duration of Infection, years	**9.4 (5.3-14.6)**	**19.0 (8.7-25.4)**	**10.3 (522-14.7)**	**19.4 (8.7-26.2)**
AST, IU/dL	**20 (17-27)**	**23 (19-32)**	**20 (18-27)**	**23 (19-32)**
ALT, IU/dL	**20 (14-28)**	**29 (19-47)**	**21 (16-35)**	**29 (20-49)**
FIB-4 ≥1.30	1.13 (0.85-1.46) 10 (35.7%)	1.15 (0.86-1.66) 29 (41.4%)	1.16 (0.83-1.43) 13 (35.1%)	1.15 (0.86-1.71) 26 (42.6%)
APRI-score >0.50	0.25 (0.20-0.30) 2 (6.9%)	0.28 (0.21-0.39) 10 (14.3%)	0.25 (0.21-0.30) 2 (5.3%)	0.29 (0.20-0.41) 10 (16.4%)
FAST score Rule-in zone	**0.05 (0.03-0.14)** **0**	**0.16 (0.07-0.28)** **5 (7.0%)**	**0.06 (0.03-0.14)** **0**	**0.20 (0.08-0.36)** **5 (8.1%)**
Liver stiffness (kPa) ≥8 kPa	5.10 (3.9-6.5) 4 (13.8%)	5.6 (4.5-7.2) 11 (15.3%)	**5.0 (3.9-6.4)** 4 (10.5%)	**5.7 (4.5-7.3)** 11 (17.5.%)

Risk factors associated to presence of NAFLD

At univariate analysis the factors associated with steatosis (CAP≥ 248 dB/m) were: **higher BMI** (by 1, OR 1.16; CI 1.03-1.30), **waist circumference (men)** (by 1 cm, OR 1.12; CI 1.03-1.21), **diabetes** (OR 3.81; CI 1.04-13.93), **triglycerides** (by 10 mg/dL, OR 1.08; CI 1.01-1.16), **duration of infection** (by one year, OR 1.09; CI 1.03 -1.15) and Fibroscan-AST **(FAST) score** (by 0.1, OR 1.46; CI 1.06-2.03).
At multivariate analysis only BMI and duration of infection were confirmed as risk factors [(OR 1.31; CI 1.12-1.54) and (OR 1.11; CI 1.03-1.19) respectively].

Risk factors associated to moderate/severe NAFLD

The risk factors associated with S2-S3 steatosis at univariate analysis were: **waist circumference (men)** (OR 1.08; 1.01-1.16), **diabetes** (OR 3.07; CI 1.04-9.04), **triglycerides** (OR 1.08; CI 1.01-1.14), **LDL-Cholesterol** (by 10 mg/dL, OR 0.86; CI 0.77-0.98), **duration of HIV infection** (OR 1.08; CI 1.02-1.13), **ever exposed to TAF** (OR 0.98; CI 0.97-0.99), **ever exposed to DTG** (OR 3.52; CI 1.50-8.26) and **FAST score** (OR 1.58; CI 1.15-2.16).

At multivariate analysis BMI, duration of infection and DTG exposure were confirmed as risk factors (OR 1.15; CI 1.00-1.33, OR 1.11; CI 1.03-1.19, and OR 3.67; CI 1.16-11.64 respectively).

Considerations

The preliminary results of our study show that metabolic risk factors are linked to NAFLD as in the general population but they also confirm that chronic antiretroviral infection plays an important role in the development of liver steatosis.

Conclusion

Longer duration of HIV infection and a higher BMI are the main drivers of NAFLD in our cohort.
A TAF- based regimen doesn't seem to expose to a greater risk of steatosis while **exposure to INSTI (especially DTG) could be associated with NAFLD severity**.
Considering the small sample size and that we only found an association with qualitative exposure to drugs, we need to collect more data to confirm our results and assess the association with INSTI exposure and liver steatosis over time.

References

[1]Michel, M., Labenz, C., Armandi, A. *et al.* Metabolic dysfunction-associated fatty liver disease in people living with HIV. *Sci Rep* **13**, 9158 (2023).
[2]Bischoff, J. *et al.* Stratifying the risk of NAFLD in patients with HIV under combination antiretroviral therapy (cART). *EClinicalMedicine*. 2021 Sep 5; 40:101116.