Plasma Proteomics Signature of People Living With HIV, With NAFLD, With and Without Obesity

Louise E. van Eekeren [1], Nadira Vadaq [1], Vasaliki Matzaraki [1], Adriana Navas [1], Elise M.G. Meeder [1], Marc J.T. Blaauw [1], Wilhelm A. Vos [2], Albert L. Groenendijk [3], Gert Weijers [1], Jan van Lunzen[1], Mihai G. Netea[1], André J.A.M. van der Ven [1], Quirijn de Mast [1], Eric T.T.L. Tjwa [1], Leo A.B. Joosten [1] for the 2000HIV Human Functional Genomics Partnership Program

[1] Radboudumc, Nijmegen, the Netherlands, [2] OLVG, Amsterdam, the Netherlands, [3] Erasmus University Medical Center, Rotterdam, the Netherlands

01619

BACKGROUND

- Obesity is an important risk factor in metabolic dysfunction-associated steatotic liver disease (MASLD, formerly known as NAFLD), but MASLD also occurs in lean PLHIV, with possible different underlying pathophysiology.
- Proteomics facilitate biomarker discovery and may help unravel biological mechanisms.

METHODS

Design

A cross-sectional data from the 2000HIV cohort

Participants

PLHIV on long-term ART, N = 1036

Methods

Transient elastography, for the assessment of

- Steatosis, controlled attenuation parameter (CAP) ≥ 248 dB/m
- Fibrosis, liver stiffness measurement (LSM) ≥ 7.0 kPa

Proteomics

- Olink® Explore, 2367 proteins

Statistical analyses

- Limma model to assess differentially expressed proteins (DEP)
- Metascape to identify functional pathways from the GO biological processes, KEGG and Reactome libraries enriched with DEP
- DEP were correlated to HIV-specific characteristics and antiretroviral therapy (ART).

Proteomic analyses indicate heightened involvement of HIV and ART in liver steatosis in lean PLHIV

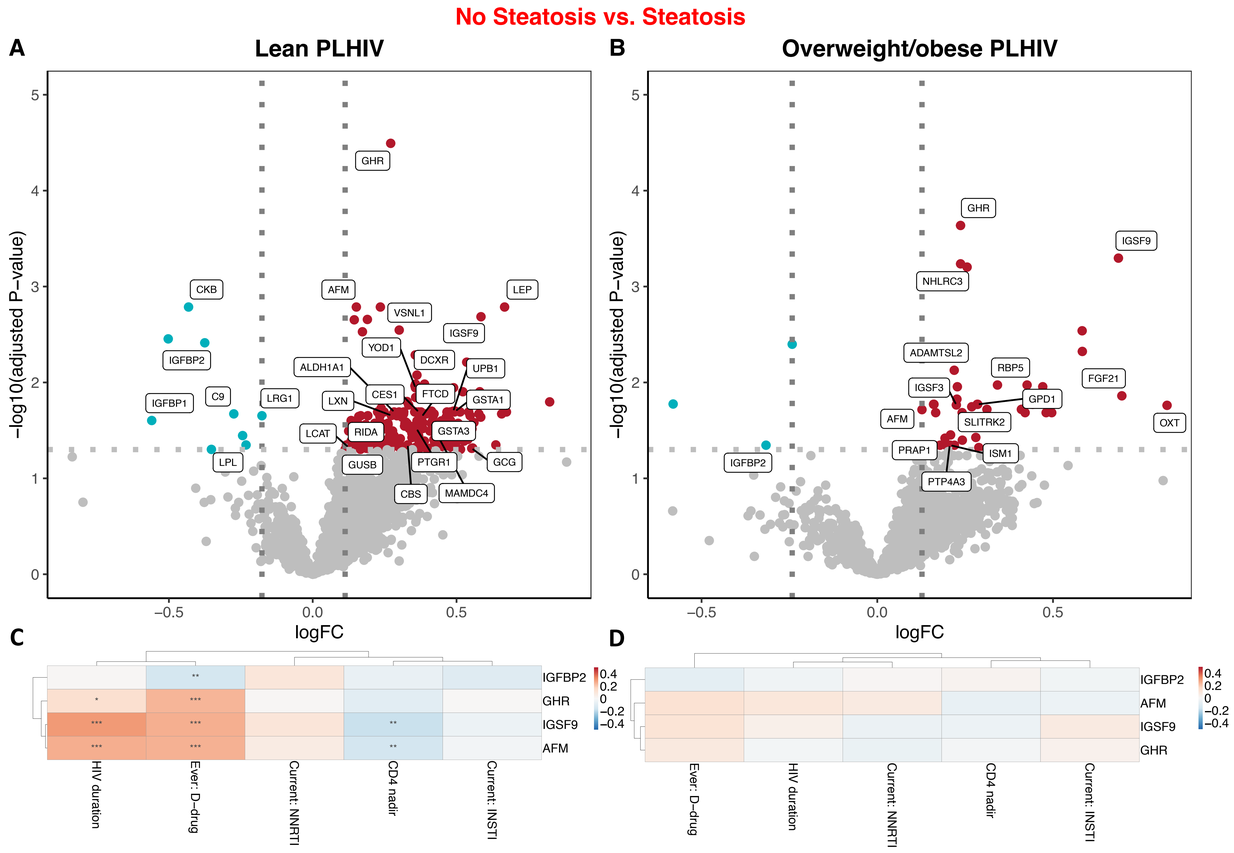

Figure A and B: volcano plot showing the results for lean (**A**) and overweight and obese PLHIV (**B**) of the differential expression analysis adjusting for age, sex, fat layer thickness and pandemic and season. Only validated proteins are annotated. **Figure C and D**: correlation plots showing the spearman correlation coefficient between the four shared DEP with a selection of HIV-related factors and ART lean (**C**) and overweight and obese PLHIV (**D**) . * P-value 0.01 - 0.05; ** P-value 0.001 – 0.01; and *** P-value < 0.001

RESULTS

	Lean (N = 463)	Overweight/obese (N = 503)
Age (yrs)	51 [41– 59]	53 [45 – 60]
Male sex	91% (423/463)	83% (419/503)
BMI (kg/m²)	22.6 [21.3 – 23.9]	27.8 [26.1 – 30.2]
Steatosis	30% (139/463)	64% (323/503)
HIV Duration (yrs)	11.1 [6.0 – 17.7]	12.0 [6.6 – 17.3]
CD4 Nadir (cells/μl)	270 [160 – 410]	260 [140 – 400]

- More DEP (n = 27) were identified in lean PLHIV with vs. those without steatosis compared to overweight/obese PLHIV (n = 15), and only four DEP were shared, i.e. insulin-like growth factor-binding protein 2 (IGFBP2), growth hormone receptor (GHR), afamin (AFM), and the novel protein immunoglobulin superfamily member 9 (IGSF9).
- Multiple DEP were associated with HIV-characteristics and ART, especially in lean PLHIV.

CONCLUSIONS

- Steatosis signatures differed between lean and overweight/obese PLHIV, with the former being more correlated with HIV-specific characteristics and ART, indicating heightened involvement of HIV-specific factors in the pathogenesis of liver steatosis in lean PLHIV
- The novel protein IGSF9 is strongly associated with MALSD

ADDITIONAL KEY INFORMATION

Louise.vanEekeren@radboudumc.nl

www.2000HIV.com

The 2000HIV study is supported by ViiV Healthcare

www.2000HIV.com