Lipidomics of metabolic dysfunction-associated steatotic liver disease post-HCV eradication in PWH

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BACKGROUND

- Direct-acting antiviral (DAA) therapy achieves sustained virologic response (SVR) in nearly all patients with HCV.
- However, liver disease progression persists in some cases despite HCV clearance, and metabolic dysfunction-associated steatotic liver disease (MASLD) may play a role in this progression.
- This study investigates lipidomic profiles linked to MASLD in HIV/HCV-coinfected patients with advanced fibrosis or cirrhosis, assessed at 1- and 6-years post-DAA-induced SVR.

METHODS

- **Participants**: 52 HIV/HCV-coinfected patients with advanced fibrosis/cirrhosis with SVR following DAA therapy.
- **Lipidomic Profiling**: Untargeted analysis was performed on plasma samples at 1 year (n=52) and 6 years (n=29) post-SVR using liquid chromatography-mass spectrometry.
- **Primary Outcome**: MASLD, defined as a Hepatic Steatosis Index ≥36 with at least one adult cardiometabolic risk factor.
- **Statistical Methods**: Analyses included orthogonal partial least squares discriminant analysis (oPLS-DA) and generalized linear models (GLM), adjusted for multiple comparisons.

Elevated PCs and TGs, coupled with reductions in LPCs and LPEs, indicate persistent metabolic imbalances that could drive liver disease progression despite achieving SVR.

PCs: Phosphatidylcholines; **TGs:** Triglycerides;
LPCs: Lysophosphatidylcholines; **LPEs:** Lysophosphatidylethanolamines

RESULTS

MASLD Prevalence post-SVR:

- 28.9% at 1 year
- 44.8% at 6 years

Lipid Profiles:

- oPLS-DA models differentiated patients by MASLD status, identifying 225 significant plasma lipids at 1 year and 167 at 6 years (VIP score ≥1).
- Adjusted GLMs showed significant associations between MASLD and 116 lipids at 1 year and 49 at 6 years.

Lipid Categories:

- At 1 year, over 75% of significant lipids were glycerophospholipids (GP), with increased phosphatidylcholines (PC) and phosphatidylethanolamines (PE), and decreased lysophosphatidylcholines (LPC) and lysophosphatidylethanolamines (LPE) (**Figure 1A**).
- At 6 years, LPC remained the most abundant differential GP, with additional decreases in lysophosphatidylinositols (LPI) and fatty acids and significant increases in triglycerides (TG) (**Figure 1B**).

Common Lipids:

- Twelve plasma lipids were consistently associated with MASLD at 1 and 6 years. (**Figure 2A**).
- All showed an inverse association with MASLD, regardless of time post-SVR (**Figures 2B–2C**).

CONCLUSIONS

- MASLD was prevalent during follow-up in this cohort, with lipidomic profiles revealing notable changes over time.
- Increased PCs and triglycerides, along with decreased LPCs and LPEs, indicate persistent metabolic disturbances potentially contributing to liver disease progression despite achieving SVR.
- These findings underscore the role of lipid dysregulation in the pathogenesis of post-SVR liver disease and highlight the importance of long-term metabolic and liver health monitoring in HIV/HCV-coinfected patients with advanced fibrosis or cirrhosis.

ADDITIONAL KEY INFORMATION

- **Keywords**: Lipidomics, MASLD, PWH, HCV eradication
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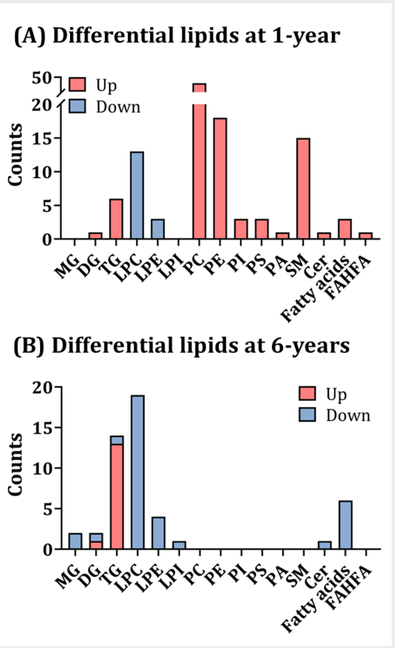


Figure 1. Lipidomic analysis in PWH following successful HCV treatment stratified by MASLD status. Counts of upregulated and downregulated differential lipids at the subclass level in MASLD vs. non-MASLD patients at 1 year (**A**) and 6 years (B) post-treatment.



Figure 2. Plasma lipids linked to MASLD at 1 and 6 years post-successful HCV treatment in PWH. (**A**) Plasma lipids associated with MASLD at 1 year and 6 years. Associations of common plasma lipids with MASLD at 1 year (**B**) and 6 years (**C**) post-treatment.

