Longitudinal Associations of Semaglutide with Liver Fibrosis Score in People with HIV

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BACKGROUND

- Metabolic dysfunction-associated steatotic liver disease (MASLD) and liver fibrosis are key drivers of morbidity and mortality in people with HIV (PWH)[1]
- Semaglutide reduces steatohepatitis and liver fibrosis in the general population[2]
- Limited evidence for clinical effectiveness and safety of semaglutide for liver fibrosis in PWH[3]

METHODS

- *Setting:* 10 geographically diverse sites of the CFAR Network of Integrated Clinical Systems (CNICS) cohort[4]
- *Inclusion:* all adult PWH initiating semaglutide for diabetes and/or weight loss with data for FIB-4 calculations (4/2018 – 11/2024)
- *Study design:* within-person, quasi-experimental, new-user analysis using linear mixed models
  - *Exposure:* semaglutide
  - *Outcome:* liver fibrosis (FIB-4 score)

$$\text{FIB-4} = \frac{\text{Age} \times \text{AST}}{\text{Platelet Count} \times \sqrt{\text{ALT}}}$$

  - Adjusted for age, birth sex, race/ethnicity, and HCV infection
  - *A priori* baseline stratifications: FIB-4, HBV infection, HCV infection, alcohol use, semaglutide dose
    - HCV infection: any lifetime reactive HCV antibody, RNA, or genotype test
    - HBV infection: any lifetime positive or detectable HBV surface antigen, DNA, or e antigen
  - Complete case analysis
- *Follow-up:* up to 4 years before semaglutide initiation until the first of: 11/2024, semaglutide discontinuation, death, or loss to follow-up

Semaglutide was associated with reductions in FIB-4 score in moderate-to-advanced liver fibrosis with the greatest declines in advanced fibrosis.

Table 1. Key baseline characteristics for the overall cohort of PWH in care at CNICS sites initiating semaglutide.

Study and Demographics	N=1850, mean follow-up: 3.7 years (SD 1.6), mean time on semaglutide: 218 days (SD 406) Mean age 52 years, 27% female, 60% non-white race/ethnicity
HIV	96% HIV RNA <200 copies/mL, mean CD4 797 cells/mm^3
Liver	No-to-Low Fibrosis (FIB-4 <1.3): 1368 (74%) Moderate Fibrosis (FIB-4 1.3-2.67): 428 (23%) Advanced Fibrosis (FIB-4 >2.67): 54 (3%) HCV: 16%[a], HBV: 7%
Cardiometabolic	80% BMI ≥30, 59% DM, 62% treated dyslipidemia, 80% treated HTN
Alcohol Use	57% reported alcohol use during previous year[a] Mean AUDIT-C[a] 1.6 (SD 2.1, range 0-12) 19% hazardous alcohol use[c]

[a]Any recent alcohol use in the previous year: AUDIT-C ≥1. Hazardous alcohol use: AUDIT-C ≥3 if female birth sex and ≥4 if male birth sex. Denominator for "Any Recent Alcohol Use" based on number of PWH completing AUDIT-C (N=1156). Denominator for hazardous alcohol use based on number of PWH with any recent alcohol use.
Abbreviations: AUDIT-C, Alcohol Use Disorders Identification Test-Consumption; BMI, body mass index; DM, diabetes mellitus; FIB-4, Fibrosis-4 score; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTN, hypertension; PWH, people with HIV; SD, standard deviation.

DISCUSSION AND CONCLUSIONS

- Semaglutide was associated with decreased liver fibrosis score in PWH who have moderate-to-advanced fibrosis and high burden of cardiometabolic conditions; the greatest decreases occurred in advanced fibrosis.
- Semaglutide appeared to have a good safety profile with respect to liver fibrosis score.
- Although no substantial differences by HBV, HCV, alcohol, and semaglutide, numbers are small so will need additional exploration in the future.
- Our findings, together with earlier studies, suggest semaglutide could play a role in managing MASLD and liver fibrosis in PWH, especially as they age and experience the longer-term impacts of cardiometabolic disease.
- Further work is needed to address access and how best to implement these therapies to maximize benefit in PWH.

PLAIN LANGUAGE SUMMARY: This study, together with earlier studies in the general population, provides evidence that semaglutide potentially may improve liver stiffness (here, measured using a blood test score) in people with HIV who have liver disease related to metabolic conditions (such as diabetes and obesity) and at least moderate liver stiffness. This benefit may be greater in individuals with more liver stiffness.

Table 2. Change in FIB-4 after semaglutide initiation using adjusted[a] linear mixed models, stratified by baseline liver fibrosis category.

Baseline Stratum	N	# Obs	ΔFIB-4	95% CI	P
Overall	1,850	18,549	0.01	-0.02, 0.04	0.6
No-to-Low Fibrosis (FIB-4 <1.3)	1,368	12,839	0.06	0.03, 0.08	<0.001
Moderate Fibrosis (FIB-4 1.3-2.67)	428	5,026	-0.05	-0.11, 0.01	0.12
Advanced Fibrosis (FIB-4 >2.67)	54	684	-0.64	-0.97, -0.30	<0.001
No-to-Moderate Fibrosis (FIB-4 ≤2.67)	1,796	17,865	0.03	0.00, 0.06	0.03
Moderate-to-Advanced Fibrosis (FIB-4 ≥1.3)	482	5,710	-0.11	-0.18, -0.05	<0.01

Table 3. Change in FIB-4 after semaglutide initiation[a] in PWH with moderate-to-advanced fibrosis using adjusted[a] linear mixed models with *a priori* stratifications.

Baseline Stratum in PWH with Moderate-to-Advanced Fibrosis		N	# Obs	ΔFIB-4	95% CI	P
Hepatitis B	**No HBV**	434	4,945	-0.13	-0.20, -0.06	<0.001
	HBV	48	765	0.03	-0.18, 0.23	0.8
Hepatitis C	**No HCV**	374	4,146	-0.13	-0.20, -0.05	<0.01
	HCV	108	1,564	-0.07	-0.22, 0.07	0.3
Recent Alcohol Use[b]	**No Alcohol Use**	149	2,043	-0.08	-0.18, 0.02	0.11
	Any Alcohol Use	168	1,682	-0.06	-0.18, 0.05	0.3
	Hazardous Use	59	525	-0.14	-0.37, 0.09	0.2
Semaglutide Dose[c]	**Low dose**	284	3,124	-0.16	-0.25, -0.07	<0.001
	High dose	46	695	-0.21	-0.43, 0.01	0.06
	Unknown dose	152	1,891	-0.01	-0.13, 0.11	0.9

[a]Models adjusted for age, birth sex, race/ethnicity, and HCV infection (when not stratified by HCV).
[b]Any recent alcohol use in the previous year: AUDIT-C ≥1. Hazardous alcohol use: AUDIT-C ≥3 if female birth sex and ≥4 if male birth sex. Denominator for "Any Recent Alcohol Use" based on number of PWH completing AUDIT-C (N=1156). Denominator for hazardous alcohol use based on number of PWH with any recent alcohol use.
[c]Low dose: semaglutide injectable 0.25, 0.5, or 1mg and oral 3 or 7mg. High dose: semaglutide injectable 1.7, 2, or 2.4mg and oral >7mg.
Abbreviations: AUDIT-C, Alcohol Use Disorders Identification Test-Consumption; FIB-4, Fibrosis-4 score; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PWH, people with HIV

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