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High burden of MASLD and metALD in People with HIV: a call for liver fibrosis screening prioritization

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Background: Evidence suggests that metabolic dysfunction-associated steatotic liver disease (MASLD) has heightened severity in people with HIV (PWH). However, hepatology guidelines do not recognize HIV as a risk factor for MASLD and fibrosis. Most data rely on the outdated NAFLD nomenclature, emphasizing the need for research within the MASLD framework.
Aim: to assess the prevalence and factors associated with steatotic liver disease (SLD), its subcategories, and significant liver fibrosis in PWH.
Methods: We analyzed data from clinical centers in Canada, Italy and Germany on consecutive PWH undergoing unselected screening for SLD and liver fibrosis. SLD was defined as controlled attenuation parameter >248 dB/m. MASLD was defined as SLD plus ≥1 cardiometabolic factor without alcohol intake >20-30g/day. Metabolic dysfunction- and alcohol-associated liver disease (MetALD) was defined as SLD with ≥1 cardiometabolic factor and alcohol intake 20-60g/day. Alcohol-associated liver disease (ALD) was defined as SLD with alcohol intake >60g/day. Cryptogenic SLD (cSLD) was defined as SLD without cardiometabolic risk factors or other causes of SLD. Significant liver fibrosis and cirrhosis were diagnosed by liver stiffness measurement >8 kPa and >13 kPa, respectively. Logistic regression was used to investigate factors associated with MASLD and fibrosis.
Results: Among 3,006 PWH (median age 53, 25% female, all on ART, 85% with undetectable HIV viral load), 14% had HCV coinfection and 3% had HBV coinfection. SLD, MASLD, MetALD, cSLD, and ALD prevalence were 43.4%, 26.2%, 9.8%, 5.2%, and 2.2%, respectively. Overall, 11.2% had significant fibrosis, and 3.5% had cirrhosis. PWH with MASLD and MetALD had a significantly higher prevalence of significant fibrosis and cirrhosis compared to those without SLD (Figure). In multivariable analysis, body mass index (OR 1.28, 95% CI: 1.21–1.32) and age >50 (OR 1.47, 95% CI: 1.07–2.08) were independently associated with MASLD after adjusting for sex, duration of HIV infection, ALT, GGT, nadir CD4 <200 cells/uL, and use of integrase inhibitors. Significant fibrosis was associated with age (OR 1.01, 95% CI: 1.00–1.06), male sex (OR 1.53, 95% CI: 1.13–2.25), MASLD (OR 2.55, 95% CI: 1.70–3.25), MetALD (OR 1.89, 95% CI: 1.17–2.99), integrase inhibitor use (OR 1.65, 95% CI: 1.17–2.24), nadir CD4 <200 cells/uL (OR 1.45, 95% CI: 1.06–1.98), and HCV coinfection (OR 3.41, 95% CI: 2.46–4.71), while HBV coinfection was not.
Conclusion: The updated SLD definition reveals a high prevalence of significant liver fibrosis in PWH, driven by hepatic steatosis with metabolic alterations (MASLD and MetALD), HIV-related factors, and HCV coinfection. PWH should be globally recognized as a high-risk population for MASLD and prioritized for liver fibrosis screening.

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Involvement of the ERG1 potassium channel in cholangiocarcinoma cell biology

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Background and Aim: Due to the lack of proper biomarkers and potentially effective treatments, the management of cholangiocarcinoma (CCA) is still challenging. In this view, ion channels have been proven to be novel biomarkers as well as new targets for cancer therapy, due to their easy druggability. The voltage-gated K+ channel hERG1 exert pleiotropic effects in cancer cells. Thus, this study explored the influence of hERG1 in intrahepatic CCA (iCCA) susceptibility.
Methods: Validation of h*ERG1* in iCCA tissues was performed in TCGA database. In vitro experiments were assessed to estimate the impact of h*ERG1 inhibition* on cell function in iCCA cell lines (HUCCT1, CCLP1, CCA4).
Results: Significant difference in h*ERG1* gene expression was observed between iCCA and normal tissue samples. Similarly, iCCA cell lines significantly showed high protein content of hERG1 compared to normal cholangiocytes (NHC3).

Treatment with E4031, a selective hERG1 inhibitor as well genetic depletion (siRNA), showed, albeit limited impact of cell growth, a substantial reduction of invasive capability of iCCA cells. Moreover, immunoprecipitation assay and immunofluorescence revealed the formation of an active macromolecular complex with $\beta 1$ integrin responsible for VEGF-A activation through the phosphorylation of AKT signaling.

Furthermore, treatment with the bispecific antibody (scDb: single-chain Diabody) that binds the hERG1-$\beta 1$ complex, negatively impacted invasiveness of iCCA cells as well as expression of epithelial to mesenchymal genes. Importantly in vitro co-treatment with scDb and cisplatin-gemcitabine, significantly reduced growth of iCCA cells.
Conclusions: This study suggests that hERG1 may play a critical role in the initiation and progression of intrahepatic CCA, highlighting its potential as a therapeutic target.

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