

Fatty liver disease in HIV: common, underappreciated, and understudied

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As the introduction of combination antiretroviral therapy (ART), HIV-infected individuals have experienced reduced morbidity from opportunistic infections and malignancies, and an increased life expectancy. With longer life, the prevalence of comorbid conditions in HIV-infected adults has increased.

Liver disease is the highest non-AIDS cause of death in HIV-infected patients, in part due to the high rates of coinfection with viral hepatitis [1,2]. Recent reports suggest a decline in liver-related deaths and, with the increasing availability of effective antiviral therapy for hepatitis B and C, further reductions in liver-related morbidity and mortality are expected. Consequently, nonalcoholic fatty liver disease (NAFLD), and the necroinflammatory, progressive form of NAFLD, non-alcoholic steatohepatitis (NASH), have emerged as increasingly frequent causes of clinically significant liver disease in HIV-infected persons.

In HIV-negative populations, NAFLD and NASH are associated with increased cardiovascular and renal disease as well as all-cause mortality [3,4]. NASH can progress to end-stage liver disease and is associated with an increased risk of hepatocellular carcinoma, even in the absence of cirrhosis [5,6]. Despite these significant clinical risks, the natural history of NAFLD and NASH in HIV-infection remains poorly understood. Further, the safety and efficacy of available preventive and therapeutic strategies for NAFLD and NASH are unstudied in HIV.

In this issue of *AIDS*, Maurice *et al.* [7] report a systematic review and meta-analysis of NAFLD, NASH, and hepatic fibrosis in HIV-monoinfected adults. Their findings are

remarkable for several reasons. First, the analysis identifies a NAFLD prevalence in HIV-monoinfected patients of 35%, higher than prevalence estimates for the general population in North America, Europe, or worldwide [8,9]. In HIV-infected patients undergoing liver biopsy for further evaluation of elevated aminotransferases, NASH was seen in 45% and significant fibrosis in 22%. In similar studies in HIV-negative populations, NASH prevalence is 12–30% and significant fibrosis in 7% [10]. Though a number of factors can influence these rates, including race and ethnicity, and the prevalence of obesity and diabetes, taken together, these findings confirm that HIV-infected patients are at high risk for NASH, fibrosis, and related complications.

Second, the meta-analysis confirms that metabolic factors, notably elevated BMI, insulin resistance, and dyslipidemia, confer the greatest increased risk of NAFLD in HIV infection, similar to the general population. CD4⁺ cell count was the only HIV-specific variable associated with NAFLD in the analysis, suggesting a role for immune recovery. Notably, age, time since HIV diagnosis, and duration of ART were not associated with increased risk.

The association with BMI is especially concerning given the rising prevalence of overweight and obesity in HIV-positive patients [11]. In one large US outpatient cohort, nearly half were overweight or obese at the time of ART initiation and 20% increased to a higher BMI category within the subsequent 2 years [12]. In a US Veterans' Affairs cohort, HIV-positive veterans gained significantly more weight 1 year after initiation of ART compared with age-matched and sex-matched HIV-negative controls [13].

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Not surprisingly, these weight changes translate to increased risk of metabolic complications. In the Veterans' Affairs cohort, weight gain was more strongly associated with increased risk of incident diabetes mellitus in HIV-positive vs. HIV-negative individuals (10 vs. 6% increased risk per 5-lb gain). In the multicohort Data Collection on Adverse Events of Anti-HIV Drugs study, weight gain in the first year after initiation of ART was associated with an increased risk of cardiovascular disease and diabetes [14]. Coupled with HIV-related inflammation and immune activation, the high prevalence of obesity places HIV-infected patients at increased risk for metabolic complications including NAFLD and NASH and highlights the need for more aggressive management of obesity and fatty liver in the aging HIV-infected population.

Perhaps most remarkable, this analysis, limited to studies including imaging or histologic confirmation of NAFLD and NASH, identified only 10 studies suitable for inclusion, and the quality of the studies, graded by the NIH Quality Assessment Tool, was moderate to poor, due to the retrospective, cross-sectional study designs and lack of longitudinal follow-up. More than 20 years after the introduction of combination ART and recognition of the complex adverse effects of ART and the associated immune recovery, assessment of fatty liver disease in HIV-positive patients remains woefully understudied. Consequently, one of the more vexing questions in HIV and NAFLD remains unanswered: what is the contribution of specific antiretroviral classes and agents to liver disease risk? One study included in the meta-analysis identified an association between steatosis with NRTIs, whereas four others did not. Integrating noninvasive assessments of liver disease into trials of ART initiation or switch studies could help define the incidence and prevalence of NAFLD and potential contribution of ART to disease progression.

As Maurice *et al.* [7] discuss, although NAFLD and NASH are common in HIV-infected adults, the absence of long-term studies limits our understanding of how disease progression compares with that in HIV-negative patients. This meta-analysis serves as a call to action for further study of NAFLD and NASH in HIV. Including assessments of NAFLD and NASH in HIV clinical trials can better define the epidemiology and natural history in HIV, a critical first step to reducing risk and improving outcomes in our patients. Longitudinal studies ideally with histologic assessments are needed to characterize the natural history of NAFLD in HIV, especially as NASH may occur with more fulminant features and at a lower BMI in HIV-infected patients [15,16].

Although awaiting additional data from trials, clinical assessment for fatty liver disease can be integrated into HIV care in most settings. Patients with metabolic risk

factors, especially those with elevated aminotransferase levels, should be evaluated and managed following guidelines for the general population [17,18]. Perhaps the most important take-home message is that persistently elevated aminotransferase levels in HIV-infected patients should not be ignored or attributed to minor ART-related toxicities. They may be the first clue to significant liver disorders that can have major clinical consequences.

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Conflicts of interest

There are no conflicts of interest.

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