Elevated Aminotransferase Levels Among HIV-Infected Persons: What’s Lurking Under the Surface?

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(See the HIV/AIDS Major Article by Morse et al on pages 1569–78.)

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Individuals infected with the human immunodeficiency virus (HIV) have experienced an unprecedented increase in life expectancy as a result of extraordinary advances in treatment and care. Nonetheless, they remain at an elevated risk for several comorbidities, one of the most important being liver disease [1]. Liver disease is common among HIV-infected persons—partly due to the shared routes of transmission of HIV and viral hepatitis. Several studies have also highlighted that HIV-monoinfected adults without hepatitis B virus (HBV) or hepatitis C virus (HCV) frequently have elevated aminotransferase levels and underlying liver disease [2, 3]. The etiology of these elevations often remains unknown and is presumptively attributed to substance use, possible antiretroviral medication effects, or HIV infection itself.

A handful of studies have investigated the causes of elevated aminotransferases among HIV-monoinfected patients, demonstrating that the most common cause is nonalcoholic fatty liver disease (NAFLD) [4–7]. NAFLD is a clinicopathologic disorder defined by the presence of fat in >5% of hepatocytes in the absence of other secondary causes (eg, alcohol use, hereditary disorders, steatogenic medications, or viral hepatitis) [8]. Nonalcoholic steatohepatitis (NASH), a subgroup of NAFLD, is defined by the presence of inflammation (ie, lobular inflammation, hepatocellular ballooning, and/or fibrosis) in addition to steatosis. Because most prior studies evaluating the causes of aminotransferase elevations among HIV patients were small [5, 6] or did not evaluate biopsy-confirmed cases [7], further studies regarding the precise etiology and pathogenesis of aminotransferrase elevations among HIV-monoinfected adults are needed.

The study by Morse et al [9] in this issue of Clinical Infectious Diseases evaluated 62 HIV-infected adults with persistently (≥6 months) elevated aminotransferase levels. Participants were receiving antiretroviral therapy for ≥1 year and were without viral coinfections (negative for HBV and HCV, and in some cases hepatitis E virus) or other known causes of liver disease. Each participant completed a robust battery of questionnaires/interviews, metabolic tests, computed tomographic (CT) imaging, and a liver biopsy.

The study found that nearly 75% of participants had NAFLD, >50% had NASH, and nearly 20% had bridging fibrosis by liver biopsy. The presence of NASH and fibrosis are especially important given their greater likelihood of progressing to liver dysfunction and hepatocellular carcinoma, and because they represent a major cause of cirrhosis of “unknown” etiology.

The high prevalence of fatty liver disease found in this study is clearly eye-opening. Prior studies among HIV patients have found notable, albeit lower, rates of NAFLD (31%–65%) and NASH (6%–26%) [4, 5, 7]. The high rates in the current study should be contextualized within study population characteristics as the prevalence of NAFLD increases with age, male sex, and specific underlying conditions. In the present study [9], the median age of participants was 50 years; 94% were men, 30% were obese, and nearly 50% had the metabolic syndrome. As many of these characteristics mirror those of today’s HIV patients, this study’s findings are relevant to practicing clinicians. Finally, although not addressed by the current study, NAFLD and NASH may exist in the setting of normal aminotransferase levels; hence, the impact of these disorders may be even greater than shown by Morse et al.

In the current study [9], NASH was associated with “traditional” risk factors of obesity and insulin resistance, findings consistent with the literature [5, 6, 8, 10]. Prior studies have additionally shown
to the general population, HIV-infected persons have progressively experienced epidemic rates of obesity and the metabolic syndrome [11], likely contributing to the high prevalence of NAFLD.

Importantly, this study found no associations between NASH and HIV-related factors including HIV duration, history of opportunistic infections, CD4 cell count, specific antiretroviral medications or duration of use. As the current study [9] did not include antiretroviral-naive participants, the overall effect of treatment could not be evaluated. Furthermore, it is unclear if the aminotransferase elevations in the current study occurred before and/or during antiretroviral use. Overall, the study’s findings concur with prior studies, which have not implicated specific HIV factors with NAFLD or NASH [4].

One study did find an association between cumulative nucleoside reverse transcriptase inhibitor exposure and NAFLD, but diagnoses were not biopsy-confirmed [7]. A subsequent study found no associations between mitochondrial function/DNA content and NASH [6]. Overall, these findings are reassuring and suggest that HIV-specific factors may not be the main culprits for aminotransferase elevations and NASH among HIV-infected adults.

Beyond potentially modifiable factors, this study found that genetic factors play a role in NASH. Examining specific genetic alleles related to triglyceride metabolism (ie, PNPLA3 gene), associations with NASH were noted among HIV-infected persons, similar to findings in the general population [12]. As such, genetic factors may contribute to the susceptibility to NAFLD/NASH and may explain some of the interindividual differences among patients with HIV.

So what are the clinical implications of this study’s findings? The study demonstrates that many HIV-monoinfected patients with elevated aminotransferase levels have significant liver pathology, most commonly due to NAFLD and/or NASH. As such, clinicians should utilize these data to bolster strategies for reducing the risk factors for NAFLD/NASH. Prior studies in the general population have demonstrated that weight loss can improve both liver steatosis and inflammation [13, 14]. In addition to weight management strategies, the recognition and treatment of insulin resistance and dyslipidemia, which may exist even among lean patients, is important. General guidelines for the management of NAFLD and NASH have been recently published [8]. Medications (eg, vitamin E or thiazolidinediones) may be considered in select patient populations with NASH [8], but their long-term safety and use among HIV-infected populations require more investigation. Overall, the presence of elevated aminotransferases among HIV patients often signifies underlying NAFLD and/or NASH, and early management, mainly through lifestyle modifications, should be considered to potentially prevent its associated complications.

Although the current study does not provide data on the long-term outcomes of NAFLD/NASH, prior studies have shown that these conditions are associated with excess mortality, most commonly due to cardiovascular disease [15, 16]. Furthermore, NASH may lead to end-stage liver disease and hepatocellular carcinoma [16, 17]. Elevated aminotransferases may be an important marker for the ongoing milieu of metabolic derangements that place patients at risk for adverse health events. For example, the fatty liver overproduces C-reactive protein, plasminogen activator inhibitor 1, and coagulation factors, while underproducing other factors such as adiponectin, thereby increasing the risk for conditions including cardiovascular disease [18]. A cross-sectional study of relatively young HIV-infected persons demonstrated a strong association between NAFLD and coronary artery calcium scores [19]. Future prospective studies should be conducted examining the long-term outcomes of NAFLD/NASH among HIV-infected vs HIV-uninfected persons, and whether its morbidity is amplified in the setting of HIV infection or factors such as antiretroviral use.

Another important question is the use of liver biopsies among HIV patients with asymptomatic, mildly elevated aminotransferases. Although liver biopsies may provide the most conclusive data of the cause and stage of disease, universal performance remains uncertain given limitations of cost, sampling error, and potential risks. The authors evaluated several noninvasive clinical and laboratory markers, but these had mostly similar and/or overlapping values between patients with and those without NASH or fibrosis. The study did find that CT findings (eg, liver-to-spleen ratio) were most predictive of biopsy-proven NASH, but such imaging requires financial and potentially health-related (radiation) costs. Unfortunately, the authors did not evaluate if combinations of clinical and laboratory factors would be helpful in predicting significant pathology. Moreover, they did not evaluate if other noninvasive tests such as transient elastography (eg, Fibroscan) or serum FibroTests (eg, NASH FibroSURE), which can detect and quantify liver fibrosis, would be beneficial.

Data available during routine clinic visits can be informative. Studies in the general population have shown that the presence of metabolic syndrome, a high NAFLD Fibrosis Score (available at http://nafldscore.com) [20], and/or ongoing >2-fold alanine transaminase elevations are useful for predicting NASH and fibrosis in patients with NAFLD, and may guide the performance of liver biopsies [8, 21]. Ultimately, the development of evidence-based guidelines for evaluating and managing elevated aminotransferase levels among HIV-infected persons are needed and best informed by further in-depth studies among large HIV cohorts.

Overall, the authors are to be commended for undertaking this study, the most comprehensive assessment of the causes and risk factors of elevated aminotransferase levels among HIV-monoinfected persons to date. Because
aminotransferase elevations are a common phenomenon among long-term HIV-infected persons, data for addressing “real world” questions about their significance are important in an effort to optimize the care of HIV patients. The study by Morse et al [9] puts us a step closer to this goal.

Significant liver disease due to NAFLD/NASH is often “lurking under the surface” of HIV patients with persistently elevated aminotransferase levels—even those without viral hepatitis coinfection and those with only low-level elevations. With the rapid evolution of drugs to cure HCV, NAFLD/NASH will likely become the dominant liver disease among HIV-infected persons. As NAFLD/NASH may not only be an important marker, but also a mediator, for a myriad of future adverse health outcomes, focused efforts on its prevention and management, namely through addressing weight and insulin resistance, should be a top priority.

Notes

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