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REVIEW

Nonalcoholic Fatty Liver Disease Among Individuals with HIV Mono-infection: A Growing Concern?

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Abstract

Purpose of Review Liver disease is a leading cause of non-AIDS-related death in the HIV population since the introduction of highly active antiretroviral treatment (HAART). Recent studies suggest that patients with HIV are at high risk for nonalcoholic fatty liver disease (NAFLD) and progressive liver fibrosis. Evidence for the prevalence, risk factors, and diagnostic methodologies of NAFLD in patients with HIV mono-infection is summarized here.

Recent Findings Although limited, published studies suggest that the prevalence of NAFLD is higher (30–50%) and progresses at an increased rate in patients with HIV compared to the general population. Identifying those at risk for significant liver fibrosis is critical, preferably with non-invasive screening tests. While there is a paucity of evidence in this population, transient elastography (TE) appears to provide a sensitive, non-invasive screening modality.

Summary Identifying NAFLD early will allow for dietary and lifestyle interventions, as well as future drug therapies to decrease the risk of progressive liver fibrosis and cirrhosis in the high-risk HIV population. Clinicians should be aware of this risk and consider using TE for NAFLD diagnosis and surveillance.

Keywords NAFLD · NASH · HIV · Transient elastography

Introduction

Since the introduction of highly active antiretroviral therapy (HAART), AIDS-related mortality has decreased, and liver disease is now a leading cause of non-acquired immunodeficiency syndrome (AIDS)-related death [1–3]. In the absence of co-infection with viral hepatitis, nonalcoholic fatty liver disease (NAFLD) has emerged as a new and growing concern in the long-term management of patients with HIV. NAFLD is defined as the accumulation of excess triglycerides in hepatocytes (steatosis) in the absence of excessive alcohol use or viral hepatitis. The spectrum of NAFLD liver disease ranges from simple steatosis to the more progressive form, nonalcoholic steatohepatitis (NASH) [4, 5].

NAFLD affects approximately 30% of the general population and is associated with increasing age and metabolic risk factors such as obesity, type 2 diabetes, hypertension, and dyslipidemia; individuals of Hispanic descent are at significantly higher risk of NAFLD progression [6–11]. In the USA, NAFLD currently has an annual direct medical cost estimated at $103 billion, which will likely increase with the continued upward obesity trend [12]. Recent studies have suggested that patients with HIV are at increased risk for the

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development and progression of NAFLD. Based upon the above, the high-risk HIV population will likely experience an increased economic and health burden. Early diagnosis can identify those at risk for NAFLD progression and creates an opportunity for lifestyle interventions to impact morbidity and mortality. However, early diagnosis can be challenging since approximately 70% of those with NAFLD have normal hepatic function tests and conventional radiological scans cannot reliably stage the severity of liver disease [13, 14]. Despite these limitations, it is critical to identify patients with HIV at risk of significant liver fibrosis, preferably with sensitive non-invasive screening tests.

This article will review the published data on the prevalence, risk factors, and clinical significance of NAFLD in patients with HIV mono-infection. Specifically, we will also discuss limitations of evidence accrued by prevailing diagnostic methodologies.

HIV and NAFLD

Prevalence

Our knowledge of the exact prevalence of NAFLD in patients with HIV is limited by the relative paucity of published studies, but previous results suggest that the prevalence is higher (30–50%) and progresses at an increased rate compared to the general population [15, 16]. A cross-sectional European study using ultrasound or elastography detected NAFLD and significant liver fibrosis (> F2) in 55% and 18% of patients with HIV, most of whom were young and non-obese [17]. In a US case–control study, patients with HIV had more fibrosis by laboratory biomarkers (APRI and FIB-4) and histology when compared to patients without HIV infection despite similar metabolic characteristics [18]. In 62 patients with HIV with persistently elevated transaminases who underwent liver biopsy, 73% had NAFLD, 55% had NASH and 16% had bridging fibrosis [19]. Two studies using TE to measure liver stiffness reported significant fibrosis (≥ 7.0 kPa) ranging from 15–27% [20, 21]. A recent meta-analysis of 10 studies enrolling HIV mono-infected patients reported the prevalence of NAFLD (diagnosed via imaging studies), NASH and fibrosis (diagnosed by biopsy) as 35%, 42%, and 22% [22]. While the above studies demonstrated a higher rate of NAFLD in the HIV-infected population, others have suggested there may be a lower prevalence. Using CT cross-sectional imaging, Price, et al. concluded that HIV-infected individuals had a lower prevalence of NAFLD compared to those without HIV [23]. In another study of 122 HIV mono-infected patients, liver fat fraction via magnetic resonance imaging and spectroscopy showed decreased steatosis in HIV women and no difference in HIV men as compared to HIV negative men and women [24]. The wide variability and overall small numbers in the current published literature highlights the importance of further investigation of this population as chronic liver disease becomes a leading cause of non-AIDS mortality.

Risk Factors

In the general population, NAFLD is associated with increased age and metabolic risk factors such as obesity, type 2 diabetes, hypertension, and dyslipidemia [6–11, 25]. Individuals with the metabolic syndrome (insulin resistance, visceral adiposity, dyslipidemia) and of Hispanic descent are at a higher risk of NAFLD progression. A similar upward metabolic syndrome and obesity trend within HIV patients [26] will likely increase the risk of NAFLD [27], but may not completely account for the increased prevalence of NAFLD and liver fibrosis reported in younger and non-obese patients with HIV [17, 18]. While the HIV population has risk factors similar to those in the general population, it is unknown if there are risk factors that are unique to the HIV-infected individual. Variants of PNPLA3, an enzyme involved in triglyceride metabolism, has been associated with hepatic fat accumulation, increased NASH severity and hepatocellular carcinoma within the general population [28–30]. A 2010 US case–control study reported an association between the rs738409 PNPLA3 polymorphism and increased NAFLD prevalence in patients with lower BMIs and decreased diabetes risk, suggestive of genetic etiologies independent of classic metabolic risk factors [31]. Furthermore, among HIV patients, prevalence of PNPLA3 variants was significantly higher in those with elevated liver enzymes and histologically confirmed NASH [19].

There are currently more than 30 different antiretroviral drugs approved for HIV treatment. As treatment paradigms evolve, it is important to highlight how therapeutic shifts have potentially impacted the incidence and prevalence of the metabolic syndrome. Some of the older antiretroviral medications were associated with dyslipidemia, insulin resistance, and/or mitochondrial toxicity, and thus could be risk factors for the development of hepatic steatosis [32]. These are now less frequently used as most patients have been transitioned to newer regimens consisting of less-toxic agents such as tenofovir alafenamide and integrase inhibitors. Although these new agents do not cause lipodystrophy or mitochondrial toxicity, there have been reports of weight gain and visceral fat accumulation associated with integrase inhibitors [33, 34].

Without adequate management, 25–40% of individuals with NAFLD may progress to the more progressive form, NASH, which can evolve to cirrhosis and hepatocellular carcinoma, with increased risk of death [4, 5]. Data for NASH-related mortality in patients with HIV are not currently available, which may be related to inaccurate ICD

coding and/or that this diagnosis is under-recognized given the overall paucity of published studies. Despite these limitations, the existing studies suggest patients with HIV are high-risk for progressive NASH. Therefore, it is critical to identify patients with HIV at risk of significant liver fibrosis.

Pathophysiology and Clinical Significance

The pathophysiology of HIV infection and the development of liver pathology is a complex, multifactorial process encompassing an imbalance of liver immune cells (Kupffer and hepatic stellate cells) resulting in hepatocyte death and fibrosis formation in a pro-inflammatory environment. These pathogenic mechanisms remain poorly understood and apply to the general population as HIV specific mechanisms have not yet been identified. An in-depth discussion of this topic has been recently reviewed and is beyond the scope of this paper [35]. In brief, NAFLD and liver fibrosis development in patients with HIV may be influenced by the culmination of several mechanisms including: (1) metabolic dysfunction characterized by excessive hepatic lipids resulting in hepatic stellate cell (HSC) activation and increased liver fibrosis risk (which may or may not be related to BMI), (2) chronic immune activation promoting liver inflammation, (3) microbial translocation/inflammation due to epithelial barrier disruption from decreased gut CD4 T-cells, and (4) mitochondrial dysfunction/injury, by direct HIV effects or some antiretrovirals, resulting in induced oxidative stress and free fatty acid accumulation. More research is needed, including a better understanding of the associated risk factors.

Cumulative evidence shows that NAFLD liver fibrosis is independently associated with increased liver-related morbidity and mortality [36], emphasizing the need for effective therapy. Weight loss is the main stay of treatment for NAFLD and has been recommended in combination with treatment of metabolic risk factors and behavioral therapy in a multidisciplinary approach [36–39]. Given the difficulties of sustained lifestyle modifications, many pharmacotherapies are undergoing evaluation. A recent review of NASH therapies provides an overview of current and developing therapeutics with their general pharmacologic targets including metabolic pathways, oxidative stress/inflammation, and antifibrotics [40]. (1) Metabolic pathways: Anti-glycemic control medications such as glucagon-like peptide (GLP-1) receptor agonists and sodium-glucose cotransporter 2 (SGLT-2) inhibitors along with 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) have demonstrated varying ability to reduce hepatic fat in NAFLD/NASH patients [41–43]. (2) Oxidative stress/inflammation: Participants treated with the antioxidant vitamin E had improved NASH histology [44]. In a recent phase 2b study, investigators noted improvements in fibrosis in NASH patients treated with an oral C–C chemokine receptor type 2 and type 5 (CCR2/5) antagonist [45]. Interestingly, CCR5 is also an HIV entry receptor. (3) Antifibrotics: In a phase 3 clinical trial (REGENERATE), the farnesoid X receptor (FXR) agonist obeticholic acid demonstrated fibrosis improvement (≥ 1 stage) without worsening of NASH at the planned 18-month analysis [46–48]. The peroxisome proliferator-activator receptor (PPAR) alpha/delta agonist Elafibranor is currently undergoing phase 3 evaluation (RESOLVE-IT) for NASH fibrosis [48, 49]. There are no approved NASH therapies available to HIV-infected individuals, as this population is excluded from current clinical trials.

As discussed above, the mechanisms are complex and not well understood. Further investigation is needed to elucidate whether the pathogenesis is due to greater inherent metabolic risk or if it is associated with unique processes in HIV infection. As anti-fibrotic medications become available, understanding these mechanisms could potentially predict therapeutic response rates. Thus, identifying HIV mono-infected individuals with liver fibrosis and enrolling them into future clinical studies could possibly reduce their risk of long-term adverse liver outcomes.

Heterogeneity of Diagnostic Methods Used and Limitations of Present Data

Early detection of NAFLD is challenging given the relatively insensitive available diagnostic methodologies. Liver enzymes can be misleading as up to 70% of NAFLD patients have normal LFTs [13, 14]. The use of liver biopsy, the diagnostic gold standard, as a screening tool is limited by its invasive nature and sampling error, and traditional radiology scans do not stage liver disease severity. Thus, the true prevalence of NAFLD in patients with HIV is not fully understood given the current literature's heterogeneity of diagnostic methods.

We will discuss the limited current data investigating the relationship between NAFLD and HIV mono-infection in those studies utilizing liver biopsy and transient elastography (Table 1).

Liver Biopsy Studies

One of the earliest prospective studies conducted by Sterling, et al. in 2013 identified 14 patients with HIV without hepatitis B/C co-infection (HBV/HCV) or significant alcohol abuse who underwent liver biopsy due to abnormal liver enzymes [50]. Steatosis and NASH were detected in 65% and 26%, respectively, demonstrating a high prevalence of NAFLD and NASH in this population with HIV mono-infection. This was the first prospective North American study to exclude HBV and HCV infected individuals, as previous investigators focused on viral hepatitis co-infection. A

Table 1 Diagnosis of NAFLD and/or liver fibrosis in HIV mono-infected patients

Study design	Study population	Country	*n*	Diagnostic modality	Findings	Comments
Prospective, cross-sectional [42]	HIV+ patients with abnormal LFTs	United States	14	Liver Biopsy	NAFLD: 65% NASH: 26% Significant Fibrosis: N/A	Steatosis and NASH were common in a small cohort of HIV patients with abnormal LFTs
Prospective, cross-sectional [16]	HIV+ patients enrolled in a naval base clinic	United States	216	Ultrasound & Liver Biopsy	NAFLD: 31% NASH:N/A Significant Fibrosis: N/A	Only 55 patients underwent biopsy
Prospective, cross-sectional [44]	HIV+ patients enrolled in a university-based clinic	Canada	202	TE, serum cytokeratin-18 & liver biopsy	NAFLD: N/A NASH: 11.4% Significant Fibrosis: 58.9%	Only 17/23 patients underwent biopsy
Prospective, cross-sectional [43]	HIV+ patients with abnormal LFTs	France	30	Liver Biopsy	NAFLD: 60% NASH: 53% Significant Fibrosis: N/A	High prevalence of NAFLD & NASH in a small cohort of HIV patients with abnormal LFTs
Multi-center prospective, cross-sectional [45]	HIV+ patients at risk for NAFLD enrolled in the ECHAM study	7 centers in Belgium, France Germany	49	Hepatic MRI-PDFF, TE, biochemical tests, & liver biopsy	NAFLD: 76% NASH: N/A Significant Fibrosis: 63%	Selective population ("at risk" for NAFLD). 64% of eligible patients deferred biopsy
Retrospective review [46]	HIV+ patients with liver biopsy performed due to abnormal LFTs	United Kingdom	97	Liver Biopsy and TE	NAFLD: 28% NASH: 33% Significant Fibrosis: N/A	TE data available for only 28% of biopsies. Significant fibrosis defined using cutoff value of ≥ 7.5 kPa
Prospective, cross-sectional [59]	HIV+ patients with abnormal LFTs	United States	66	Liver Biopsy/TE	NAFLD: 72.6% NASH: 64% Significant Fibrosis: N/A	25/59 (42%) of patients screened with TE had increased liver stiffness
Prospective, cross-sectional [20]	HIV+ patients enrolled in a university-based clinic	Canada	300	Transient Elastography	NAFLD: 48% NASH: N/A Significant Fibrosis: 15%	Predominantly male population. 35% overweight and 20% obese
Prospective, cross-sectional [60]	HIV+ patients on HAART ≥ 6 months enrolled in the PROSPEC-HIV study	Brazil	395	Transient Elastography	NAFLD: 35% NASH: N/A Significant Fibrosis: 9%	Fibrosis defined using higher cutoff value of ≥ 8 kPa
Cross-sectional, case-control [21]	HIV+ patients enrolled in general ID and HIV metabolic clinics	China	80	Transient Elastography & ^{1}H-MRS	NAFLD: 28.8% NASH: N/A Significant Fibrosis: 14.3%	Fibrosis defined using cutoff value of 7.0 kPa

HIV human immunodeficiency virus, *LFTs* liver function tests, *NASH* nonalcoholic steatohepatitis, *NAFLD* nonalcoholic fatty liver disease, *TE* transient elastography, *ECHAM* European Cohort on HIV, Aging and Metabolic Liver Disease, *MRI-PDFF* magnetic resonance imaging proton density fat fraction, *kPa* kilopascal, ^{1}*H-MRS* proton-magnetic resonance spectroscopy, *HAART* highly active antiretroviral therapy

prospective cross-sectional study by Morse, et al. detected NAFLD in 73% of 62 HIV mono-infected patients with abnormal LFTs, with 55% of patients demonstrating NASH [19]. Ingiliz, et al. found NAFLD and NASH in 60% and 53% of 30 HIV mono-infected patients [51]. Benmassaoud, et al. combined transient elastography and serum cytokeratin-18 with confirmation liver biopsy in 202 participants. Although only 17 patients underwent biopsy, 58.9% had F2-F4 disease [52]. In early 2019, Lemoine, et al. utilized multiple diagnostic modalities including liver biopsy in only 49 patients of the 140 enrolled. 76% had NAFLD with 63% having clinically significant fibrosis (F2-F4) [53].

While much of the data discussed above demonstrated a > 50% prevalence in the population with HIV mono-infection, others have reported lower rates. A cross-sectional study by Crum-Cianflone, et al. used ultrasound and liver biopsy to detect NAFLD in 36% of 216 patients, although only 55 patients underwent biopsy [16]. A retrospective study found only 28% of 97 patients with HIV mono-infection had biopsy-confirmed NAFLD [54]. A recent meta-analysis found the prevalence of NAFLD, NASH and fibrosis was 35%, 42%, and 22% in patients with HIV mono-infection, although only 10 studies of moderate–poor quality were included and used a variety of diagnostic modalities (imaging and biopsy) [22].

Although many of these investigators reported an increased prevalence of NAFLD and liver fibrosis in patients with HIV mono-infection, there are several limitations. First, all studies had relatively small sample sizes. Liver biopsy, while the gold standard for NAFLD/liver fibrosis diagnosis, is invasive and may be influenced by sampling error and observer variations in staging [55, 56]. Results of this procedure represent only 1/50,000 of the liver and may lead to under-reporting of non-homogenous liver disease severity [57]. Finally, the above studies primarily recruited patients with abnormal liver enzymes. Since the majority of NAFLD patients have normal liver enzymes, these publications likely underestimated the prevalence [13, 14]. As such, more sensitive and accurate non-invasive tools have been (and continue to be) developed to diagnose and monitor NAFLD/NASH outcomes.

Transient Elastography Studies

Transient elastography (TE) via Fibroscan has become an important non-invasive modality for the diagnosis of NAFLD/NASH. While the diagnostic accuracy in HIV patients is unknown, TE is widely available, cost effective, provides quick point of care results and has a negative predictive value of 98% (95% CI 97–99) [58]. TE consists of using an ultrasound probe that transmits vibrations through liver tissue [59]. The velocity of wave propagation is related to liver stiffness and correlated with fibrosis. The examination requires fasting for 2–3 h and takes as little as 5–10 min. Fibroscan allows a more global assessment with measurements encompassing liver tissue volume approximately 100 times bigger than biopsy, which reduces the sampling error. Controlled attenuation parameter (CAP) is coupled to the Fibroscan and allows for non-invasive liver fat quantification, a hallmark of NAFLD/NASH associated with increased metabolic syndrome rates. Compared to blood tests, recent studies in NAFLD patients show TE had the highest AUROC (0.83–0.86) for non-invasive fibrosis classification and the highest sensitivity (> 88%) for advanced fibrosis diagnosis [59–61]. Inaccurate readings can be produced if valid measurements are not obtained, a situation usually occurring in patients with obesity or small intercostal spaces, or from operator inexperience [62]. Although most studies evaluating TE sensitivity and specificity focused mainly on HCV patients, many recent studies have confirmed the accuracy and usefulness of TE in staging disease severity among other chronic liver diseases [63–66]. Herein, we will discuss studies utilizing TE as a diagnostic tool in those with HIV mono-infection.

A prospective study employed TE with CAP to detect NAFLD and significant liver fibrosis in 48 and 15% of 300 HIV mono-infected patients [20]. Increased liver stiffness was observed in 64% of 33 patients screened with TE, all of whom had elevated LFTs and biopsy confirmed steatohepatitis [67]. Utilizing proton-magnetic resonance spectroscopy and TE to screen 80 Asian HIV mono-infected individuals, 27% of those with NAFLD had significant fibrosis as defined by a cutoff value of 7.0 kPa [21]. A larger Brazilian cohort of 395 patients using TE with CAP detected 35% NAFLD and only 9% fibrosis using a higher cutoff value of ≥ 8 kPa [68].

Elastography technology has been available for almost 30 years, yet it has only recently been studied to further delineate its role in liver disease as investigators search for a non-invasive alternative to liver biopsy. TE has emerged as an essential non-invasive tool for the diagnosis of NAFLD/NASH. The small number of studies investigating this role in the HIV mono-infected population is limited in size and heterogenous design. However, evidence from other populations suggests that dissemination of this technology will provide a sensitive, non-invasive screening modality in a cohort at high risk for NAFLD and progressive liver fibrosis.

Conclusions and Future Studies

Since the advent of HAART, morbidity and mortality from non-AIDS-related chronic diseases have increased [69]. There is a higher prevalence of liver disease among HIV individuals, and although HIV co-infection with HBV and/or HCV contributes significantly to chronic liver disease, recent studies suggest that HIV mono-infected individuals are at

high risk for NAFLD and liver fibrosis [50]. The responsible pathogenic mechanisms remain poorly understood, but it may be related to immune mediated processes and metabolic risk factors [35, 70]. NAFLD is projected to be the leading cause for orthotopic liver transplantation in the USA with an economic burden estimated to exceed $103 billion [12, 71]. Identifying NAFLD early will allow for targeted interventions, particularly lifestyle modification, to decrease the chance of progressive fibrosis and cirrhosis [72]. The current literature in the HIV population is sparse and limited by the absence of prospective studies to monitor the progression of liver disease. Both Infectious Diseases and Gastroenterology providers should remain aware of this increased risk and consider using non-invasive tools such as TE for diagnosis and surveillance.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interests.

References

1. Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996–2006: collaborative analysis of 13 HIV cohort studies. *Clin Infect Dis*. 2010;50:1387–1396.
2. Weber R, Sabin CA, Friis-Møller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. 2006;166:1632–1641.
3. Lewden C, May T, Rosenthal E, et al. Changes in causes of death among adults infected by HIV between 2000 and 2005: The "Mortalité 2000 and 2005" surveys (ANRS EN19 and Mortavic). *J Acquir Immune Defic Syndr (1999)*. 2008;48:590–598.
4. Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology*. 2005;129:113–121.
5. Luis Calzadilla B, Adams LA. The natural course of non-alcoholic fatty liver disease. *Int J Mol Sci*. 2016;17:774.
6. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther*. 2011;34:274–285.
7. Williams CD, Stengel J, Asike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology*. 2011;140:124–131.
8. Marchesini G, Babini M. Nonalcoholic fatty liver disease and the metabolic syndrome. *Minerva Cardioangiol*. 2006;54:229–239.
9. Pagano G, Pacini G, Musso G, et al. Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association. *Hepatology (Baltimore, MD)*. 2002;35:367–372.
10. Armstrong MJ, Adams LA, Canbay A, Syn WK. Extrahepatic complications of nonalcoholic fatty liver disease. *Hepatology*. 2014;59:1174–1197.
11. Younossi ZM, Stepanova M, Afendy M, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clin Gastroenterol Hepatol*. 2011;9:524–530.
12. Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. *Hepatology (Baltimore, MD)*. 2016;64:1577–1586.
13. Fracanzani AL, Valenti L, Bugianesi E, et al. Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: a role for insulin resistance and diabetes. *Hepatology (Baltimore, MD)*. 2008;48:792–798.
14. Mofrad P, Contos MJ, Haque M, et al. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. *Hepatology*. 2003;37:1286–1292.
15. Giovanni G, Nicola S, Chiara S, et al. Nonalcoholic fatty liver disease in HIV-infected patients referred to a metabolic clinic: prevalence, characteristics, and predictors. *Clin Infect Dis*. 2008;47:250–257.
16. Crum-Cianflone N, Dilay A, Collins G, et al. Nonalcoholic fatty liver disease among HIV-infected persons. *J Acquir Immune Defic Syndr (1999)*. 2009;50:464–473.
17. Lombardi R, Sambatakou H, Mariolis I, et al. Prevalence and predictors of liver steatosis and fibrosis in unselected patients with HIV mono-infection. *Dig Liver Dis*. 2016;48:1471–1477.
18. Vodkin I, Valasek MA, Bettencourt R, Cachay E, Loomba R. Clinical, biochemical and histological differences between HIV-associated NAFLD and primary NAFLD: a case-control study. *Aliment Pharmacol Ther*. 2015;41:368–378.
19. Morse CG, Matthews L, Kovacs JA, et al. Nonalcoholic steatohepatitis and hepatic fibrosis in HIV-1-monoinfected adults with elevated aminotransferase levels on antiretroviral therapy. *Clin Infect Dis*. 2015;60:1569–1578.
20. Vuille-Lessard E, Lebouche B, Lennox L, et al. Nonalcoholic fatty liver disease diagnosed by transient elastography with controlled attenuation parameter in unselected HIV monoinfected patients. *AIDS*. 2016;30:2635–2643.
21. Lui G, Wong VWS, Wong GLH, et al. Liver fibrosis and fatty liver in Asian HIV-infected patients. *Aliment Pharmacol Ther*. 2016;44:411–421.
22. Maurice JB, Patel A, Scott AJ, et al. Prevalence and risk factors of nonalcoholic fatty liver disease in HIV-monoinfection. *AIDS (London, England)*. 2017;31:1621–1632.
23. Price JC, Seaberg EC, Post WS, et al. Risk factors for fatty liver in the multicenter AIDS cohort study. *Am J Gastroenterol*. 2014;109:695–704.
24. Kardashian A, Ma Y, Scherzer R, et al. Sex differences in the association of HIV infection with hepatic steatosis. *AIDS (London, England)*. 2017;31:365–373.
25. Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology (Baltimore, MD)*. 2004;40:1387–1395.
26. Koethe JR, Jenkins CA, Lau B, et al. Rising obesity prevalence and weight gain among adults starting antiretroviral therapy in the United States and Canada. *AIDS Res Hum Retrovir*. 2016;32:50–58.
27. van der Schouw YT, Peeters PH. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet*. 2016;387:10026.
28. Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet*. 2008;40:1461–1465.
29. Liu YL, Patman GL, Leathart JBS, et al. Carriage of the **PNPLA3** rs738409 C>G polymorphism confers an increased risk of

non-alcoholic fatty liver disease associated hepatocellular carcinoma. *J Hepatol*. 2014;61:75–81.
30. Sookoian S, Pirola CJ. Meta-analysis of the influence of I148 M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. *Hepatology (Baltimore, MD)*. 2011;53:1883–1894.
31. Speliotes EK, Butler JL, Palmer CD, et al. PNPLA3 variants specifically confer increased risk for histologic nonalcoholic fatty liver disease but not metabolic disease. *Hepatology (Baltimore, MD)*. 2010;52:904–912.
32. Bourgi K, Rebeiro PF, Turner M, et al. Greater weight gain in treatment-naive persons starting dolutegravir-based antiretroviral therapy. Clin Infect Dis 2019. https://doi.org/10.1093/cid/ciz407.
33. Gange SJ, Kitahata MM, Saag MS, et al. Cohort profile: The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). *Int J Epidemiol*. 2007;36:294–301.
34. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed Aug 2019.
35. Debes JD, Bohjanen PR, Boonstra A. Mechanisms of accelerated liver fibrosis progression during HIV infection. *J Clin Transl Hepatol*. 2016;4:328–335.
36. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2015;149:389–397.
37. Scherer A, ois Dufour J-F. Treatment of non-alcoholic fatty liver disease. *Dig Dis*. 2016;34:27–31.
38. Thoma C, Day CP, Trenell MI. Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: a systematic review. *J Hepatol*. 2012;56:255–266.
39. Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. *Diabetologia*. 2012;55:885–904.
40. Banini BA, Sanyal AJ. Current and future pharmacologic treatment of nonalcoholic steatohepatitis. *Curr Opin Gastroenterol*. 2017;33:134–141.
41. Petit JM, Vergès B. GLP-1 receptor agonists in NAFLD. *Diabetes Metab*. 2017;43:28–30.
42. Patoulias D. SGLT-2 inhibitors: are they a promising treatment option in T2DM patients with NAFLD? *Acta Med (Hradec Kralove)*. 2017;60:167–170.
43. Dongiovanni P, Petta S, Mannisto V, et al. Statin use and non-alcoholic steatohepatitis in at risk individuals. *J Hepatol*. 2015;63:705–712.
44. Kowdley KV, Wilson LA, Van Natta ML, Pai RK, Sanyal AJ. LP10: Efficacy and safety of vitamin E for nonalcoholic steatohepatitis: combined analysis of three controlled trials. *J Hepatol*. 2015;62:S268.
45. Friedman SL, Ratziu V, Harrison SA, et al. A randomized, placebo-controlled trial of cenicriviroc for treatment of nonalcoholic steatohepatitis with fibrosis. *Hepatology*. 2018;67:1754–1767.
46. Ratziu V, Sanyal AJ, MacConell L, et al. Regenerate: a phase 3, double-blind, randomized, placebo-controlled multicenter study of obeticholic acid therapy for nonalcoholic steatohepatitis. *J Hepatol*. 2016;64:S294–S295.
47. Intercept. Intercept announces positive topline results from pivotal phase 3 REGENERATE study of obeticholic acid in patients with liver fibrosis due to NASH. 2019. Available at http://ir.interceptpharma.com/node/12371/pdf.
48. Shetty A, Syn WK. Current treatment options for nonalcoholic fatty liver disease. *Curr Opin Gastroenterol*. 2019;35:168–176.
49. Burke A. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Yearb Gastroenterol*. 2006;2006:262–264.
50. Sterling RK, Smith PG, Brunt EM. Hepatic steatosis in human immunodeficiency virus: a prospective study in patients without viral hepatitis, diabetes, or alcohol abuse. *J Clin Gastroenterol*. 2013;47:182–187.
51. Ingiliz P, Valantin MA, Duvivier C, et al. Liver damage underlying unexplained transaminase elevation in human immunodeficiency virus-1 mono-infected patients on antiretroviral therapy. *Hepatology (Baltimore, MD)*. 2009;49:436–442.
52. Benmassaoud A, Ghali P, Cox J, et al. Screening for nonalcoholic steatohepatitis by using cytokeratin 18 and transient elastography in HIV mono-infection. *PLoS ONE*. 2018;13:e0191985.
53. Lemoine M, Assoumou L, De Wit S, et al. Diagnostic accuracy of noninvasive markers of steatosis, NASH, and liver fibrosis in HIV-monoinfected individuals at risk of nonalcoholic fatty liver disease (NAFLD): results from the ECHAM study. *J Acquir Immune Defic Syndr (1999)*. 2019;80:e86–e94.
54. Prat LI, Roccarina D, Lever R, et al. FRI-465—Aetiology and severity of liver disease in HIV positive patients with suspected NAFLD: lessons from a cohort with available liver biopsies. *J Hepatol*. 2018;68:S572–S573.
55. Regev A, Berho M, Jeffers LJ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol*. 2002;97:2614–2618.
56. Maharaj B, Bhoora IG. Complications associated with percutaneous needle biopsy of the liver when one, two or three specimens are taken. *Postgrad Med J*. 1992;68:964–967.
57. Sumida Y. Limitations of liver biopsy and non-invasive diagnostic tests for the diagnosis of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *World J Gastroenterol*. 2014;20:475.
58. Mahady SE, Macaskill P, Craig JC, et al. Diagnostic accuracy of noninvasive fibrosis scores in a population of individuals with a low prevalence of fibrosis. *Clin Gastroenterol Hepatol*. 2017;15:1453–1460.
59. Wilder J, Patel K. The clinical utility of FibroScan((R)) as a noninvasive diagnostic test for liver disease. *Med Devices (Auckl)*. 2014;7:107–114.
60. Boursier J, Vergniol J, Guillet A, et al. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. *J Hepatol*. 2016;65:570–578.
61. De Silva S, Li W, Kemos P, et al. Non-invasive markers of liver fibrosis in fatty liver disease are unreliable in people of South Asian descent. *Frontl Gastroenterol*. 2017;2017:2017–100865.
62. Castéra L, Foucher J, Bernard PH, et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. *Hepatology (Baltimore, MD)*. 2010;51:828–835.
63. Sandrin L, Fourquet B, Hasquenoph J-M, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol*. 2003;29:1705–1713.
64. Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. *Gastroenterology*. 2008;134:960–974.
65. Corpechot C, El Naggar A, Poujol-Robert A, et al. Assessment of biliary fibrosis by transient elastography in patients with PBC and PSC. *Hepatology (Baltimore, MD)*. 2006;43:1118–1124.
66. Laharie D, Zerbib F, Adhoute X, et al. Diagnosis of liver fibrosis by transient elastography (FibroScan) and non-invasive methods in Crohn's disease patients treated with methotrexate. *Aliment Pharmacol Ther*. 2006;23:1621–1628.
67. Morse CG, McLaughlin M, Proschan M, et al. Transient elastography for the detection of hepatic fibrosis in HIV-monoinfected

adults with elevated aminotransferases on antiretroviral therapy. *AIDS*. 2015;29:2297–2302.
68. Perazzo H, Cardoso SW, Yanavich C, et al. Predictive factors associated with liver fibrosis and steatosis by transient elastography in patients with HIV mono-infection under long-term combined antiretroviral therapy. *J Int AIDS Soc*. 2018;21:11.
69. Puoti M, Moioli MC, Travi G, Rossotti R. The burden of liver disease in human immunodeficiency virus-infected patients. *Semin Liver Dis*. 2012;32:103–113.
70. Kaspar MB, Sterling RK. Mechanisms of liver disease in patients infected with HIV. *BMJ Open Gastroenterol*. 2017;4:e000166.
71. Allen AM, Talwalkar JA, Van Houten HK, Sangaralingham LR, McCoy RG. Healthcare cost and utilization in nonalcoholic fatty liver disease: real-world data from a large U.S. claims database. *Hepatology*. 2018;68:2230–2238.
72. Shaker M, Tabbaa A, Albeldawi M, Alkhouri N. Liver transplantation for nonalcoholic fatty liver disease: new challenges and new opportunities. *World J Gastroenterol*. 2014;20:5320–5330.