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FATTY LIVER DISEASE (V AJMERA, SECTION EDITOR)

HIV-Associated NAFLD: Disease Burden and Management

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Abstract

Purpose of Review Highly potent anti-retroviral therapy (ART) for the treatment of human immunodeficiency virus (HIV) has led to dramatic improvements in quality of life and lifespan in persons living with HIV (PLWH). PLWH, however, are suffering from other comorbid conditions, including non-alcoholic fatty liver disease (NAFLD). This review summarizes the epidemiology and pathophysiology of NAFLD in PLWH and explores unique diagnostic and treatment considerations in this population.

Recent Findings Though it is well established that there is a high prevalence of NAFLD in PLWH, the mechanisms underlying NAFLD in this population are just beginning to be explored. Traditional NAFLD risk factors, including insulin resistance, visceral adiposity, and genetics, have been consistently linked with NAFLD in PLWH. In addition, HIV-related factors including mitochondrial dysfunction, microbiome alterations, and direct effects of the virus and of ART may play a role.

Summary Given the burden of NAFLD in PLWH, further studies are necessary to investigate mechanisms specific to HIV with which to target therapies.

Keywords Human immunodeficiency virus · Non-alcoholic fatty liver disease · Non-alcoholic steatohepatitis · Anti-retrovirals · Persons living with HIV

Abbreviations

HIV	Human immunodeficiency virus
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
ART	Anti-retroviral therapy
PLWH	Persons living with HIV

Introduction

Human immunodeficiency virus (HIV) remains a major global health burden. It is estimated that in 2017 there were approximately 36.9 million people worldwide living with HIV/AIDS. In addition, an estimated 1.8 million individuals became newly infected with HIV in 2017—about 5000 new infections per day [1]. Fortunately, there has been a significant reduction in HIV-related mortality among persons living with HIV (PLWH) due to the effectiveness of anti-retroviral therapy (ART).

There has been an increase, however, in the proportion of patients dying from other non-AIDS causes [2]. By 2030, it is estimated that more than 80% of PLWH will have at least one age-related comorbidity and about 30% will have at least three age-related comorbidities [3]. Of these, liver disease is one of the biggest causes of non-AIDS-related morbidity and mortality. Although excessive alcohol consumption and comorbid viral hepatitis traditionally have contributed most to liver disease in the HIV population, non-alcoholic fatty liver disease (NAFLD) is becoming increasingly recognized as a significant etiologic factor [4]. This review will focus on the epidemiology and pathogenesis of NAFLD in PLWH and will explore diagnostic techniques and therapeutic interventions specific to this population.

Epidemiology of NAFLD Among Persons Living with HIV

NAFLD refers to hepatic steatosis in the absence of excessive alcohol use, viral hepatitis, drug exposures, or other causes of

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liver disease. NAFLD encompasses a wide spectrum of disease manifestations ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, or cirrhosis [5]. The majority of individuals with NAFLD have simple steatosis, which is defined on liver histology by the accumulation of fat in more than 5% of hepatocytes with or without mild lobular inflammation [6]. However, a subset have NASH, which is characterized by the presence of steatosis and cellular injury, demonstrated by hepatocyte ballooning and lobular inflammation. Over time, NAFLD can lead to hepatic fibrosis with progression to cirrhosis and decompensated liver disease and is one of the most common indications for liver transplantation in the adult population [7-8].

NAFLD affects an estimated 25% of the US general population, although prevalence rates vary depending on the specific population screened [9]. NAFLD is similarly common among PLWH. Table 1 summarizes prevalence estimates of NAFLD in PLWH in cross-sectional studies conducted over the past 15 years and across various populations—the estimates range from 13 to 76% [10–23]. A systematic review and meta-analysis that included five of these studies including 1256 participants reported a NAFLD prevalence of 35% (95% CI 29–42) [24••]. It is important to note, however, that these studies were conducted in populations with varying prevalence of NAFLD risk factors and using differing non-invasive techniques to diagnose NAFLD, including ultrasound, computed tomography (CT), magnetic resonance spectroscopy (MRS), and FibroScan with controlled attenuation parameter (CAP).

The gold standard for distinguishing NASH from simple steatosis remains the liver biopsy. Among PLWH with biopsy-confirmed NAFLD, evidence suggests that NASH prevalence is high, ranging from 26 to 64% (Table 2) [25–31]. In a meta-analysis including six of these studies and 208 participants with liver biopsy, the pooled prevalence of NASH was 42% (95% CI 22–64) [24••]. These studies, however, are prone to selection bias, as most subjects were biopsied due to abnormal liver enzymes. Liver biopsy studies of HIV-uninfected populations with NAFLD have similar limitations, and therefore, it is difficult to compare the histologic severity of NAFLD among people with and without HIV infection. Despite this, there is still evidence to suggest that the prevalence of NASH and advanced fibrosis is higher among PLWH [30].

Pathogenesis of NAFLD in the Setting of HIV Infection

Risk Factors Associated with Primary NAFLD

In order to understand the role of HIV in the pathogenesis of fatty liver among PLWH, it is helpful to understand the pathogenesis of NAFLD more generally. The exact mechanism by

Table 1 Prevalence of NAFLD in PLWH

Study (year)	Country	Number of subjects	Population studied	Steatosis assessment	Prevalence of NAFLD
Hadigan, C (2007)	USA	33	General HIV population	MR spectroscopy	42%
Moreno-Torres A (2007)	Spain	29	General HIV population	MR spectroscopy	58%
Guaraldi, G (2008)	Italy	225	Metabolic clinic	CT	37%
Crum-Cianflone, P (2009)	USA	216	HIV clinic	Ultrasound	31%
Nishijima, T (2014)	Japan	435	HIV clinic	Ultrasound	31%
Price, JC (2014)	USA	465	Multi-center AIDS Cohort Study (MACS)	CT	13%
Macias, J (2014)	Spain	505	HIV clinic	CAP	40%
Lui, G (2016)	China	80	Infectious disease clinic and metabolic clinic	MR spectroscopy and transient elastography	29%
Lombardi, R (2017)	Greece	125	HIV clinic	Transient elastography	55%
Vuielle-Lessard et al. (2016)	Canada	300	HIV clinic	CAP	48%
Price, JC (2017)	USA	122	Women's Interagency HIV Study (WIHS)	MR spectroscopy	28%
Kardashian, A (2017)	USA	229	Women's Interagency HIV Study (WIHS)	MR spectroscopy	29%
Perazzo, H (2018)	Brazil	395	PRO-SPEC-HIV Study	CAP	35%
Lemoine, M (2019)	Belgium, France, Germany	420	European Cohort on HIV (ECHAM)	MRI proton-density-fat fraction (MRI-PDFF), FibroScan/CAP	76%

Table 2 Prevalence of NASH in PLWH

Study (year)	Indication for biopsy	Country	Number of subjects	Prevalence of NASH
Lemoine, M (2006)	Unexplained elevated transaminases	France	14	57%
Mohammed, SS (2007)	Elevated liver transaminases and suspected NAFLD	Canada	26	55%
Ingiliz, P (2009)	Elevated liver transaminases for > 6 months	France	30	53%
Sterling, RK (2013)	> 1 abnormal liver enzyme for > 6 months	USA	14	26%
Morse, CG (2015)	Aminotransferase levels > upper limit normal for > 6 months while receiving ART	USA	62	55%
Vodkin, I (2015)	Liver biopsy database	USA	66	64%
Prat, I (2019)	Abnormal transaminases	UK	97	30%

which NAFLD leads to liver damage and fibrosis is not entirely understood. Initially, it was believed to be a "two-hit" mechanism, whereby a metabolic alteration, such as insulin resistance, leads to simple hepatic steatosis and a second hit, whether it be genetic or environmental, leads to mitochondrial dysfunction and oxidative stress, thereby triggering the progression to liver fibrosis and cirrhosis [32]. However, it is now well recognized that there are "multiple hits" contributing to NAFLD pathogenesis and progression, including insulin resistance, mitochondrial damage, and alterations to the microbiome.

Insulin resistance has long been associated with NAFLD—in the 1990s, researchers found that patients with NAFLD had insulin sensitivity and hepatic glucose production that was as impaired as type 2 diabetics [33]. Moreover, hepatic macrophages secrete inflammatory mediators, such as TNF-alpha and interleukin-1-beta, which lead to systemic insulin resistance. The excessive hepatic lipid accumulation seen in NAFLD further promotes these macrophages to exacerbate insulin resistance and to incite hepatic inflammation and fibrogenesis [34, 35]. This cycle of lipid accumulation, insulin resistance, and fibrosis has been implicated in cirrhosis and end-stage liver disease.

Mitochondrial dysfunction, including depletion of mitochondrial DNA or mitochondrial beta-oxidation, is also associated with NAFLD development [36]. These changes lead to impairment in several bioenergetic reactions involved in oxidative phosphorylation, resulting in the generation of reactive oxygen species [37]. Reactive oxygen species induce further mitochondrial damage, thereby creating a cycle by which mitochondrial dysfunction leads to further oxidative damage to mitochondrial structure and function, as well as other cellular components [38].

Finally, the microbiome has been implicated in NAFLD pathogenesis. The connection between gut microbiota and the liver was first described in the 1920s by Hoefert and his group, who reported that patients suffering from chronic liver disease had altered gut flora [39]. Multiple studies have since examined what is now referred to as the gut-liver axis. Because the majority of the liver's blood supply comes from the intestine through the portal vein, the intestinal blood supply exposes the liver to various microbiota and food products [40]. Alterations in the gut microbiota and intestinal barrier function, caused by a variety of factors including increased consumption of obesogenic foods, lead to metabolic endotoxin production, microbial translocation, and hepatic inflammation each of which can contribute to NAFLD [41].

HIV-Associated NAFLD Mechanisms

Several of the same factors that contribute to NAFLD in the general population also play a role in the development of NAFLD in PLWH. Metabolic factors, including visceral adiposity, and insulin resistance have consistently been strongly associated with NAFLD in PLWH [15]. Importantly, the prevalence of the metabolic syndrome, including obesity, dyslipidemia, increased waist circumference, and diabetes, is on the rise among PLWH [42]. The high prevalence of insulin resistance in the setting of HIV may be secondary to ongoing immune activation with high levels of pro-inflammatory markers or to expansion of CD8+/HLA-DR+ subtype T cells [43, 44]. Multiple studies have demonstrated an association between the insulin resistance seen in HIV and development of fatty liver [15, 27]. Additionally, HIV has been associated with dyslipidemia, including higher triglyceride and free fatty acid levels and lower HDL levels, which has also been associated with the accumulation of fat in the liver and can lead to fibrosis progression [45, 46].

Similar to the general population, the microbiome is also thought to play a role in the development of NAFLD in PLWH. Though there have been no human studies examining the microbiome of PLWH in relation to the development of NAFLD, there is sufficient knowledge about alterations in microbiota in PLWH to suggest that it may play a role. HIV infection is associated with damage to the gastrointestinal tract and depletion of gut CD4+ T cells, leading to dysfunction of the epithelial barrier [47]. In the setting of this dysfunction, microbial products and potentially microbes themselves may translocate from the lumen to the liver via the portal vein and have been linked to immune activation and inflammation [48]. This gut translocation of bacteria could play a role in hepatic steatosis and fibrosis progression in PLWH.

There are several mechanisms by which HIV may directly or indirectly contribute to hepatic fibrosis in the setting of co-existing viral hepatitis [49]. Whether similar mechanisms impact the severity and progression of NAFLD among PLWH is unclear and remains an important knowledge gap in the field of HIV and NAFLD. For example, HIV can infect hepatic macrophages, known as Kupffer cells, and HIV-infected Kupffer cells exhibit an exaggerated pro-fibrogenic response to lipopolysaccharide [50]. In addition, it is unclear whether HIV itself may directly cause hepatic steatosis. Loss of mitochondrial DNA has been documented in the peripheral blood mononuclear cells from HIV patients who were never exposed to ART, suggesting a possible effect of the HIV infection itself on mitochondrial function [51, 52].

Lastly, there are several factors specific to HIV treatment that have been implicated in the development of NAFLD. Liver toxicity is one of the most common serious adverse events associated with ART. ART can contribute to NAFLD in PLWH both directly (for example via mitochondrial dysfunction) and indirectly through unfavorable metabolic changes.

Nucleoside reverse transcriptase inhibitors (NRTIs) may indirectly increase the risk of NAFLD via lipid profile alterations and insulin resistance through mitochondrial toxicity. They inhibit the replication of mitochondrial DNA thereby leading to the inability to perform oxidative phosphorylation. This in turn leads to the formation of reactive oxygen species which could damage mitochondrial DNA further. This mitochondrial dysfunction can lead to adipocyte apoptosis and peripheral lipodystrophy. It also leads to the inability to oxidize free fatty acids and triglyceride accumulation within the hepatocytes [53, 54]. Older NRTIs such as didanosine (ddI) and stavudine (d4T) have been implicated in the development of metabolic syndrome NAFLD and for this reason are no longer recommended in most treatment guidelines [55]. More modern NRTIs, such as tenofovir or lamivudine, are less likely to cause mitochondrial toxicity and are thus less likely to contribute to NAFLD.

Protease inhibitors (PIs) can also induce insulin resistance and dyslipidemia, albeit through different mechanisms. Some data suggest the ability for certain PIs to directly inhibit insulin secretion from beta cells [56]. PIs can also lead to an increase of apolipoprotein B, which transports LDL- and VLDL-cholesterol and triglycerides in the circulation [57]. One study demonstrated that patients treated with PIs had higher VLDL and apolipoprotein B pool sizes and production rates compared to those on non-PI-containing regimens [58]. All of these effects can contribute to the development of NAFLD.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTI), and entry inhibitors appear to have more favorable metabolic profiles and have been less likely to be associated with NAFLD or progression of fibrosis. In fact, one study demonstrated that switching from PIs or NNRTIs to maraviroc, an entry inhibitor, decreased total cholesterol and triglycerides in a small randomized clinical trial [59]. However, there have been reports of weight gain with INSTI-based regimens [60]. Whether this potential ART-related increase in weight and visceral adiposity may contribute to the development of NAFLD remains unclear.

Diagnosis of NAFLD in Persons Living with HIV

Given the relative lack of data specific to PLWH, clinicians often must rely on NAFLD diagnostic recommendations for the general population when diagnosing and working up fatty liver in PLWH. While liver biopsy remains the gold standard for the diagnosis and staging of NAFLD, it is invasive, costly, and prone to sampling error. Furthermore, it is difficult to use liver biopsy for longitudinal monitoring. Therefore, noninvasive methods often play a large role in diagnosing and risk stratifying patients with NAFLD.

NAFLD is typically initially suspected in patients with unexplained liver enzymes or fatty liver on abdominal ultrasound. Importantly, liver enzyme elevations alone are insufficient to stage disease severity as they do not correlate well with histological findings. Moreover, many patients with NAFLD have normal liver enzymes [61, 62]. Other laboratory-based tests for fatty liver include the SteatoTest, fatty liver index, and the NAFLD liver fat score [63, 64]. All three of these tests incorporate various parameters including T2DM, BMI, triglycerides, or AST/ALT ratio. The performance of these tests, however, is suboptimal [65].

Noninvasive imaging techniques to detect hepatic steatosis include ultrasound, controlled attenuation parameter (CAP) with transient elastography, and computed tomography (CT)- or magnetic resonance imaging (MRI)-based techniques. Ultrasound has a sensitivity of 85% and specificity of 94% for the detection of NAFLD and is commonly used in clinical practice [66]. CAP is conveniently obtained simultaneously with transient elastography, although the optimal cut-offs for detecting fatty liver appear to vary depending on characteristics of the underlying population [67, 68]. Non-contrast CT is rarely used in clinical practice to diagnose NAFLD, but can detect moderate or greater steatosis. [69]. Finally, MRI-based imaging has emerged as the non-invasive gold standard for hepatic steatosis, although its cost and lack of widespread availability limit its use [70].

There have been only a handful of studies to date evaluating these noninvasive diagnostic techniques specifically in PLWH. One recent study examined several different noninvasive techniques among 49 ART-controlled HIV-monoinfected individuals with persistently elevated liver enzymes, metabolic syndrome, or lipodystrophy who underwent liver biopsy [23]. The authors found that MRI with proton density fat fraction (PDFF) and CAP were accurate for the diagnosis of steatosis with area under the receiver operating characteristic curves (AUROCs) of 0.98 (95% CI 0.96 to 1.00) and 0.88 (0.76 to 0.99), respectively. The same study also found that among the noninvasive fibrosis surrogates, APRI and FIB-4 performed best at detecting ≥F2 fibrosis, whereas FibroTest and transient elastography had low AUROCs [23]. In contrast, a prior study including 66 HIV-monoinfected individuals who underwent liver biopsy found that transient elastography detected ≥F2 fibrosis with relatively high diagnostic accuracy, with an AUROC 0.93 (95% CI 0.86 to 0.99) [71].

Future larger studies are necessary to determine the optimal modality and cut-offs for diagnosing and risk stratifying PLWH with suspected NAFLD. Currently, the American Association for the Study of Liver Diseases (AASLD) does not recommend screening for NAFLD among high-risk groups [72••]. However, the European AIDS Clinical Society recommends that those newly diagnosed with HIV be tested for all viral hepatitides as well as for liver enzyme abnormalities, including an initial determination of ALT/AST, alkaline phosphatase, and bilirubin. They further recommend that liver enzymes be repeated every 3–12 months on subsequent clinic visits [73] and that physicians screen for NAFLD with ultrasound among high-risk patients with metabolic syndrome [74].

Treatment of NAFLD

Few studies have examined treatment of NAFLD in PLWH. Therefore, recommendations have been extrapolated from the evidence-based approaches used in the general population with NAFLD. However, it is important to recognize that most NAFLD intervention studies excluded PLWH.

Lifestyle modifications are the mainstay of treatment of NAFLD. Weight reduction of at least 7–10% total body weight was associated with resolution of NASH in 90% of individuals and ≥ 1 fibrosis stage improvement in 45% in a prospective cohort study [75], and is the recommended target for improvement in liver enzymes and histology [76••]. Although this degree of weight loss could be difficult to sustain, even a more modest weight loss of 5% of initial body weight can reduce steatosis, improve liver enzymes, and offer health benefits such as reduction in hemoglobin A1c or decreased risk of developing type 2 diabetes [77, 78].

In addition to weight loss, adherence to the Mediterranean diet, a diet characterized by a high intake of olive oil, nuts, fruits and legumes, vegetables, and fish, has been associated with improvement in hepatic steatosis and insulin sensitivity in those with NAFLD [79]. In this diet, about 40% of calories are derived from fats, mostly monounsaturated fat (MUFA) and omega-3 polyunsaturated fatty acids (PUFA), both of which are associated with increased insulin sensitivity, reduced hepatic triglyceride content, and improved lipid profiles. In addition to improving liver parameters, the Mediterranean diet also has been shown to reduce the risk of cardiovascular disease and diabetes, which are two conditions that are highly prevalent in individuals with NAFLD. In fact, currently, the Mediterranean diet is the dietary pattern recommended by EASL-EASD-EASO clinical practice guidelines for patients with NAFLD [76••]. AASLD does not make recommendations related to specific macronutrient diets, but does advise a calorie-restricted diet that is successful in achieving sustained weight loss [72••].

Aside from weight loss and dietary changes, exercise even without weight loss has demonstrated decreased odds of developing fatty liver [75, 80]. In one study, patients with biopsy-proven NAFLD were randomized into lifestyle modification groups, including moderate exercise either alone or in combination with dietary modification; all interventions lead to histologic improvement in NAFLD activity scores [81]. The type of exercise performed (aerobic, resistance, or high intensity intermittent) appears to have similar effects on liver fat [82, 83]. It does not appear that more vigorous exercise holds additional benefits, though few studies have been conducted long term [84–86].

Given the evidence supporting lifestyle interventions, the EASL-EASD-EASO clinical practice guidelines currently recommend structured programs aimed at lifestyle changes towards healthy diet and habitual physical activity in those with NAFLD (C2 evidence) [76••]. Similarly, AASLD recommends moderate-intensity exercise along with a hypocaloric diet [72••]. Data supporting these recommendations among PLWH and NAFLD are lacking. A dietary intervention trial among PLWH and NAFLD aimed at increased energy expenditure and reduced caloric intake with an emphasis on long-term lifestyle and behavioral change is currently enrolling (NCT03913351). The primary outcome will be resolution of NAFLD as determined by proton-magnetic resonance spectroscopy.

Given that lifestyle interventions can be difficult to achieve and sustain, considerable effort has been dedicated to the discovery of pharmacotherapies to treat the disease. These therapies have been aimed at the patients at highest risk for liver disease progression—those with NASH and/or significant fibrosis. Many target particular aspects of NAFLD including insulin resistance, oxidative stress, inflammation, or hepatic fat accumulation. In the randomized placebo-controlled PIVENS trial, 800 IU daily of vitamin E was associated with a higher rate of improvement in the NAFLD activity score, but not in fibrosis. Also in the PIVENS trial, pioglitazone, an insulin-sensitizing agent, led to improvement in histologic steatohepatitis, but this effect did not reach statistical significance. Importantly, this study excluded PLWH [87]. Additionally, the long-term safety of these drugs among PLWH is unclear. Some studies have reported an increase in cardiovascular events, hemorrhagic stroke [88], and prostate cancer [89] with vitamin E and significant weight gain [90], loss of bone mineral density [91], and increased risk of heart failure exacerbations [92] and bladder cancer [93] with pioglitazone. Two trials are currently examining the therapeutic role of vitamin E in PLWH with NAFLD. One, conducted at McGill University Health Center, is evaluating improvement in NASH as diagnosed by liver enzymes, FibroScan/CAP measurements, and CK-18 levels with the administration of vitamin E 800 IU once daily for 6 months (NCT03988725). Another randomized trial is comparing vitamin E 800 IU daily for 24 weeks to placebo and examining percent change in liver fat content by MRI-PDFF in PLWH with NASH (NCT03669133).

Most clinical trials of investigational NAFLD compounds exclude PLWH, and therefore, it remains unknown whether they may be beneficial in this population. Cenicriviroc (CVC), a chemokine receptor type 5 (CCR5) and chemokine receptor type 2 (CCR2) antagonist, is of special interest. In a randomized trial conducted in HIV-negative individuals with NASH, more patients in the CVC arm experienced ≥ 2 fibrosis stage improvement without worsening of NASH at year 2 compared to the placebo arm, although this was not statistically significant. [94•, 95]. CVC also resulted in reduction in multiple markers of inflammation including IL1b, CCRP, IL6, and fibrinogen, as well as reduction in soluble CD14 and increase in the ligands for CCR2 and CCR5. Though it has not been studied in HIV and NAFLD, CVC has both in vitro and in vivo anti-HIV activity. Therefore, if studied in PLWH, patients should be concurrently on suppressive ART therapy [96, 97].

Recognizing the unmet need for NAFLD therapeutics among PLWH, recently, some trials have specifically addressed pharmacologic therapies in this population. The ARRIVE Trial evaluated aramchol, a fatty acid and bile acid conjugate, over 12 weeks in patients with HIV-associated NAFLD. Aramchol inhibits stearoyl-coenzyme A desaturase 1 (SCD1), a key enzyme in fatty acid synthesis. Inhibiting SCD1 has been demonstrated to decrease synthesis of and increase beta-oxidation of fatty acids, causing a decreased storage of fatty acids [98]. A previous study found a significant reduction in hepatic fat content in NAFLD patients, without HIV, after 12 weeks of 300 mg aramchol daily, compared to placebo [99]. However, in the ARRIVE Trial, 600 mg of aramchol daily did not reduce hepatic fat or body fat and muscle composition, as assessed using MRI-based measures in patients with HIV-associated NAFLD [100•].

Tesamorelin is a human growth hormone (GH)-releasing factor analog that is FDA-approved for HIV-associated lipodystrophy. It has been shown to impact hepatic fat content independent of changes in weight, potentially via oxidation of visceral fat or reduction in hepatic lipogenesis [101]. There is currently an ongoing multi-center randomized, double-blind, placebo-controlled clinical trial in PLWH and NAFLD to assess response in hepatic fat content. The initial results from the preliminary phase of the study demonstrated that liver fat, as measured by magnetic resonance spectroscopy, decreased by 32% in the tesamorelin arm while it increased by 5% in the placebo arm ($p = 0.02$) (NCT02196831).

In addition to pharmacologic therapy for the treatment of HIV-associated NAFLD and NASH, there are potentially modifiable factors specific to PLWH which may ameliorate the risk of fibrosis progression. ART choice may play a role in progression of liver disease to fibrosis among PLWH who have NAFLD. Although formal guidance is lacking, given the NRTI link to insulin resistance and lipid profile alterations through mitochondrial toxicity, it may be beneficial to avoid this class of ARTs in patients with NAFLD or to choose agents with more favorable metabolic profiles. Similarly, there may be benefit in avoiding PIs. A recent study found that switching from a ritonavir-boosted PI-based regimen to raltegravir led to a significantly greater decrease in hepatic steatosis as measured by controlled attenuation parameter (CAP) compared to those with unchanged ART and lifestyle modification only [102]. Further studies evaluating the impact of modern ART regimens on NAFLD incidence, progression, and regression are needed to guide management of this population.

Finally, given the effect of HIV on the microbiome and the gut-liver axis, one can hypothesize that altering or manipulating this axis with probiotics, antibiotics, and prebiotics could impact progression of liver disease [103]. Studies in humans using a probiotic, VSL#3, a mixture of eight lactic acid bacterial species, have demonstrated improvement in liver enzymes including reduction in AST and ALT levels in patients with NAFLD [104]. Rifaximin, which is a non-systemically absorbed antibiotic that has been tested in small prospective observational cohort studies in patients with NAFLD, has been studied in patients with HIV [105]. In these patients, rifaximin use resulted in increased microbial translocation and had direct anti-inflammatory effects independent of its effect on the gut microbiome [106]. Though the impact of this activation and translocation on the liver, specifically, was not studied, this is an area that would be important for future investigation.

Conclusions

Although the epidemiologic estimates vary widely depending on the diagnostic technique and population studied, it is evident that NAFLD is common among PLWH. While there have been increased efforts to understand the pathophysiology of

NAFLD specifically in PLWH in order to target unique treatment approaches, critical knowledge gaps remain. Future studies are necessary to better characterize the natural history of NAFLD in PLWH, develop diagnostic algorithms unique to this population, and evaluate NAFLD interventions in PLWH so as to mitigate NAFLD-associated morbidity and mortality in this high-risk population.

Compliance with Ethical Standards

Conflict of Interest: Alyson Kaplan declares no potential conflicts of interest.

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•• Of major importance

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