Title

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Journal

Clinical Gastroenterology and Hepatology, 20(2)

ISSN

1542-3565

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Publication Date

2022-02-01

DOI

10.1016/j.cgh.2020.10.018

Peer reviewed

HHS Public Access

Author manuscript

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2023 February 01.

Published in final edited form as:

Clin Gastroenterol Hepatol. 2022 February ; 20(2): 256–268. doi:10.1016/j.cgh.2020.10.018.

Expert Panel Review on Nonalcoholic Fatty Liver Disease in Persons With Human Immunodeficiency Virus

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Abstract

Nonalcoholic fatty liver disease (NAFLD) affects 25% of adults in the general population and is a disease spectrum ranging from steatosis to nonalcoholic steatohepatitis (NASH) to end-stage liver disease. NAFLD is an independent risk factor for cardiovascular disease, diabetes mellitus, and all-cause mortality, and NASH cirrhosis is a frequent indication for liver transplantation. In persons with human immunodeficiency virus (PWH), chronic liver disease is the second leading cause of non–human immunodeficiency virus–related mortality. Between 20% and 63% of PWH have NASH, and 14% to 63% have NASH with fibrosis. However, little is known about the optimal diagnostic strategies, risk factors for, and treatment of NAFLD in PWH. Here, we review

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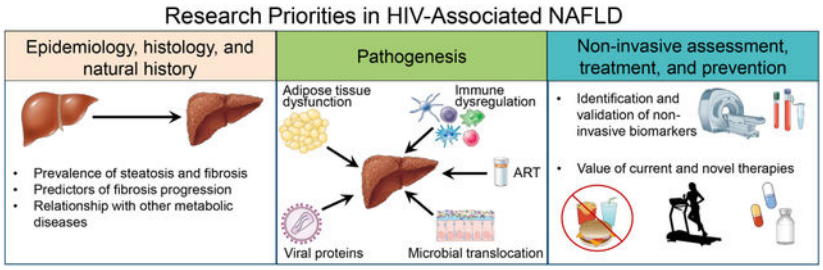
Conflicts of interest

These authors disclose the following: Kathleen E. Corey has received grant support from Bristol-Myers Squibb, Novartis, and Boehringer-Ingelheim, and has consulted for Novo Nordisk, Bristol-Myers Squibb, and Gilead; and Jordan E. Lake has received research support from Gilead Sciences, CytoDyn, Pfizer, and OncoImmune, and has served as a consultant to Merck. The remaining authors disclose no conflicts.

current data on and identify knowledge gaps in the epidemiology, pathophysiology, diagnosis, and management of NAFLD in PWH and highlight priorities for research.

Graphical Abstract



Keywords

Human Immunodeficiency Virus (HIV); Nonalcoholic Fatty Liver Disease (NAFLD); Nonalcoholic Steatohepatitis (NASH); Antiretroviral Therapy (ART); Persons With HIV (PWH)

Nonalcoholic fatty liver disease (NAFLD), affecting 25% of adults,[1] is a spectrum including steatosis (excess lipid accumulation in hepatocytes) and nonalcoholic steatohepatitis (NASH; defined by steatosis, lobular inflammation, and hepatocyte ballooning). Fibrosis may develop and progress to cirrhosis and hepatocellular carcinoma. NASH cirrhosis is a frequent indication for liver transplantation worldwide. Furthermore, NAFLD strongly is associated with insulin resistance (IR), hypertension, and dyslipidemia, and is an independent risk factor for cardiovascular disease (CVD), diabetes mellitus (DM), and all-cause mortality.[2,3]

Among persons with human immunodeficiency virus (PWH), chronic liver disease is the second leading cause (13%) of non–human immunodeficiency virus (HIV)-related mortality.[4] Furthermore, obesity, DM, and the metabolic syndrome (MetS) are prevalent in PWH, increasing NAFLD risk. Between 20% and 63% of PWH have NASH, and 14% to 63% have fibrosis.[5-7] However, little is known about the optimal diagnostic strategies, risk factors for, and treatment of NAFLD in PWH. This article reviews current data on and identifies knowledge gaps in the epidemiology, pathophysiology, diagnosis, and management of NAFLD in PWH and highlights research opportunities and priorities.

Nonalcoholic Fatty Liver Disease Prevalence and Risk

In populations without HIV (primary NAFLD), NAFLD prevalence varies from 25% of adults globally to 95% of bariatric surgery patients.[8] The strongest risk factors include obesity, DM, hypertension, and dyslipidemia,[1] with NAFLD often referred to as the hepatic manifestation of the MetS. In reality, the NAFLD/MetS relationship is bidirectional, with NAFLD being a strong predictor of future DM and CVD.[2,9] Race and ethnicity influence NAFLD risk, with Hispanics at highest risk and non-Hispanic blacks at lowest risk,[10] differences are mediated in part by genetic factors (eg, *PNPLA3* gene single-nucleotide polymorphisms).[11]

HIV-associated NAFLD (HIV NAFLD) shares risk factors with primary NAFLD.[12] In a meta-analysis, PWH with NAFLD were more likely to have DM, hypertension, and an increased body mass index (BMI).[13] Although obesity is associated consistently with NAFLD in PWH, in a study of biopsy-confirmed NAFLD, PWH had a significantly lower mean BMI, suggesting PWH may have a higher prevalence of "lean NAFLD"[14] than the general population. Indeed, in a cohort of PWH with hepatic steatosis, 45% had a BMI less than 30 kg/m^2.[15] PWH also may have lipodystrophy (increased visceral adipose tissue [AT] with or without central subcutaneous AT accumulation or peripheral lipoatrophy), and/or generalized obesity. Lipodystrophy shares cardinal features of NAFLD including IR and dyslipidemia, and may contribute to HIV NAFLD.[14] Similar to primary NAFLD, *PNPLA3* single-nucleotide polymorphisms are associated strongly with NAFLD in PWH.[6,12]

Although HIV per se is not associated with increased NAFLD risk in observational data,[12,16,17] a higher prevalence of NASH and hepatic fibrosis have been observed in HIV vs primary NAFLD.[5] Published studies of NAFLD epidemiology in PWH are summarized in Table 1. Briefly, with few exceptions, the available observational data report prevalence rates greater than 30% by imaging or biopsy, with frequent short-term progression of disease in the subset of longitudinal studies. The complexity and incomplete understanding of NASH pathogenesis make assessing the contribution of HIV and antiretroviral therapy (ART) in these settings difficult. Specifically, multiple molecular pathways may contribute, the perturbations of which are unlikely to be uniform across patients. Furthermore, to date, clinical studies have insufficiently investigated and targeted the pathways most likely to play a role in HIV NAFLD. Potential HIV- and ART-associated contributors to NAFLD are discussed in greater detail later.

Nonalcoholic Fatty Liver Disease Pathophysiology in Persons With Human Immunodeficiency Virus

Multiple pathways have been implicated in the development and progression of NAFLD in PWH and are represented in Figure 1.

Immunodeficiency and Immune Activation

Altered immune function may impact the intrahepatic inflammatory milieu and contribute to NAFLD. HIV infects macrophages and T lymphocytes, altering the hepatic microenvironment. Exposure of hepatocytes and hepatic stellate cells to HIV induces transforming growth factor-β[18] and promotes oxidative stress.[19] Furthermore, in HIV, macrophage populations shift to an anti-inflammatory, profibrotic M2 phenotype.[20]

Early immunologic insults after HIV acquisition, including gut barrier breach and selective $CD4^+$ T-cell depletion enteropathy, drive translocation of microbial products into the circulation. These changes are not fully reversed with ART and peripheral immune reconstitution, permitting persistent inflammatory disturbances.[21] Lipopolysaccharide induces hepatic tumor necrosis factor-α, promoting fibrogenesis, and activates Toll-like receptor 4 receptors on Kupffer cells, promoting inflammation and fibrogenesis. Circulating lipopolysaccharide promotes IR, liver triglyceride accumulation, and AT inflammation.[22]

These combined insults can lead to the development of hepatic inflammation, hepatocellular injury, and fibrosis characteristic of NASH.

Adipose Tissue Dysfunction

AT dysfunction, including adipocyte hypertrophy[32] and subcutaneous AT fibrosis, results in a number of detrimental immune-metabolic effects in PWH and may contribute to the development and progression of NAFLD. PWH experience AT disruptions including generalized obesity, visceral AT accumulation, and lipodystrophy. Obesity and visceral adiposity are common in PWH and have traditional and HIV-/ART-associated contributors. Although 67% or less of adult PWH are overweight or obese by BMI criteria,[23-25] increased visceral AT-to-BMI ratios[26] in PWH lead to an underestimation of total adiposity. Thus, visceral adiposity is believed to be a more accurate predictor of metabolic disease, including NAFLD risk, in PWH.[12] As in the general population, obesity and visceral AT accumulation are associated with increased systemic and tissue-level inflammation and activation of the renin-angiotensin system,[35,36] further promoting IR and cardiometabolic disease, including NAFLD.[27,28]

Other contributors to AT dysfunction include direct ART effects,[29] HIV itself,[30] and microbial translocation.[22,31] Mitochondrial dysfunction from older ART agent exposure may contribute to AT disturbances (see later).[32,33] Suppressive ART can improve fibrosi[33] (presumably from a reduction in the proinflammatory stimulus of HIV viremia) but not adipocyte hypertrophy, which promotes IR and local tissue inflammation. HIV itself induces peroxisomal proliferator-activated receptor-γ inhibition and glucocorticoid-receptor activation, inducing impaired adipocyte differentiation, accelerated lipolysis, macrophage infiltration, and hepatic steatosis.[34] HIV-associated hormonal imbalances (eg, hypogonadism) and gut microbiome alterations may play adjunctive roles.[37,38] Aging-associated central AT redistribution, adipocyte senescence, and chronic inflammation[39] may be enhanced in PWH. The overlap between contributors to/consequences of AT dysfunction in PWH[29,40] and the known contribution of AT dysfunction to NAFLD[41] sets the stage for a NAFLD epidemic among PWH.

Antiretroviral Therapy and Nonalcoholic Fatty Liver Disease

The majority of data on the contribution of ART to NAFLD are based on older, more toxic agents. Although contemporary ART generally is not believed to cause the same severity of metabolic effects, some toxicities of older ART agents, including mitochondrial toxicity, peripheral subcutaneous lipoatrophy, and their sequelae, are fully or partially irreversible. This legacy effect impacts NAFLD risk among long-term survivors of HIV and/or PWH in resource-limited settings where these agents may continue to be used.

The role of first-generation protease inhibitors (PIs) in NAFLD development remains uncertain, with associations varying by drug and population studied.[44-46] PIs are known to impact mechanisms linked to hepatic steatosis, including dramatically increasing central adiposity and altering plasma lipid profiles through inhibition of lipogenesis, decreased hepatic clearance of very-low-density lipoproteins, and increased hepatic triglyceride

production.[42,43] Thus, although results on the relationship between PIs and NAFLD conflict, biologically they are likely to contribute to NAFLD development.

Older nucleoside reverse transcriptase inhibitors (NRTIs) also may contribute to NAFLD pathogenesis through increased mitochondrial toxicity, IR, and visceral adiposity.[47] In addition, both NRTIs and non-NRTIs affect adipogenesis and adipocyte differentiation,[29] leading to mitochondrial injury, adipocyte death, and free fatty acid and triglyceride accumulation,[47-50] which contribute to the development of hepatic steatosis, IR, and systemic and tissue-level inflammation.

Contemporary ART may contribute to hepatic steatosis by promoting obesity and/or visceral adiposity. ART initiation is associated with weight gain,[40] with persons with the highest pre-ART HIV-1 RNA or lowest $CD4^+$ T lymphocyte counts at risk of greatest weight gain.[51,52] The integrase strand transfer inhibitors (INSTIs), first-line therapy for most PWH, may be associated with greater weight gain after ART initiation than other agents/classes.[53-55] In addition, risk may vary by INSTI agent and concomitant NRTI use. Multiple studies have implicated dolutegravir as associated with greater weight gain after ART initiation or switch than elvitegravir or raltegravir.[56-58] Less data are available for bictegravir, although weight gain is expected to be similar to dolutegravir.[57] Risks for weight gain with initiation of or switch to INSTIs are not well understood, but may include female sex and black race.[56,57,59]

In summary, some older ART agents are associated with hepatic steatosis, and the legacy effects of these agents, including lipodystrophy and mitochondrial dysfunction, persistently affect NAFLD risk for exposed persons. Observed associations between contemporary ART and NAFLD vary, in large part owing to differences in study design and analysis, although contemporary ART generally is not believed to carry the same risk.

Diagnosis

Steatosis can be identified by several imaging modalities, including ultrasound, noncontrast computed tomography scan, magnetic resonance imaging (MRI), and controlled attenuated parameter (CAP). Once steatosis is identified, further evaluation is required to assess for hepatic fibrosis.

Noninvasive tools (NITs) including predictive models, serum-based assays, and radiologic studies can be used to identify and stage hepatic fibrosis. The NAFLD Fibrosis Score, Fibrosis-4 (FIB-4) score, aspartate aminotransferase–to-platelet ratio index are predictive models that can estimate an individual's risk of advanced fibrosis in primary NAFLD. However, aspartate aminotransferase–to-platelet ratio index, FIB-4, and NAFLD Fibrosis Score have variable performance in PWH.[62,63] These scores include platelet count as a marker of portal hypertension, but may be less accurate in PWH owing to multiple causes of thrombocytopenia. Similarly, increased aminotransferase levels and IR often have causes other than NASH and fibrosis in PWH, compromising the specificity of these tests. The Enhanced Liver Fibrosis score is a serum-based test that estimates fibrosis through measurement of extracellular matrix markers and, although it holds promise for risk stratification in primary NAFLD, it has not been validated in PWH.

Radiographic NITs of hepatic fibrosis, which estimate the elasticity of the liver as a surrogate for fibrosis, include transient elastography (FibroScan, EchoSens, Paris, France), sheer wave elastography, and MR elastography, which have conflicting performance characteristics in studies including PWH.[63,64] Research to identify accurate circulating biomarkers for NASH and fibrosis and to comprehensively evaluate noninvasive imaging for steatosis and fibrosis diagnosis is desperately needed in PWH. A summary of the limited number of studies comparing noninvasive testing with diagnosis by liver biopsy in PWH with and without hepatitis C virus (HCV) co-infection is presented in Table 2. Briefly, most available studies are in the setting of HIV-HCV coinfection. Among these studies, MRI proton-derived fat fraction performs best (area under the receiver operating characteristic curve, 0.98) for the diagnosis of steatosis, and transient elastography performs best for fibrosis (area under the receiver operating characteristic curve, 0.61–099), although not all available modalities have been tested for each disease state (eg, no MR assessment of fibrosis). Liver biopsy, the gold standard for the diagnosis and staging of NAFLD, can distinguish steatosis from NASH, identify secondary causes of liver disease, and stage fibrosis. Although liver biopsy is limited by sampling error, risk of complications, and low provider and patient acceptance, it should be pursued when NITs indicate a high likelihood of advanced fibrosis or the etiology of liver disease remains unclear.

Screening

Screening for NAFLD, even among high-risk groups including PWH, remains controversial. The American Association for the Study of Liver Diseases[60] does not recommend screening high-risk groups for NAFLD.[61] However, the European Acquired Immune Deficiency Syndrome Clinical Society recommends screening all PWH and MetS for NAFLD with ultrasound and, if positive, perform follow-up evaluation of liver enzymes and predictive scores and/or serum fibrosis markers (http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf). However, the impact of NAFLD screening in high-risk PWH on outcomes has not yet been studied.

Histology

As in primary NAFLD, NAFLD in PWH begins with macrovesicular steatosis. Ballooning injury, characterized by enlarged hepatocytes with irregularly clumped and cleared cytoplasm, indicates NASH. Perisinusoidal fibrosis, usually from central veins alongside balloon cells, is present early in disease. As fibrosis progresses, perisinusoidal fibrosis becomes more pronounced and fibrous septations extend from portal areas. Eventually, bridging fibrosis develops, connecting periportal and pericentral strands. Cirrhosis is present when bridging fibrosis encircles nodules of hepatocytes. Disease may fluctuate, leading to various combinations of steatosis, inflammation, ballooning, and fibrosis on biopsy, complicating diagnosis. NASH and advanced fibrosis are prevalent in PWH, with a recent meta-analysis showing a 42% NASH prevalence, with 22% having bridging or more severe fibrosis.[13] However, there are no known features on liver biopsy that distinguish primary NAFLD/NASH from HIV NAFLD/NASH.

Treatment

Lifestyle intervention remains the foundation of treatment for primary and HIV NAFLD. In primary NAFLD, weight loss of 10% or more of total body weight is associated with NASH resolution in 90% of patients and a 1-stage fibrosis reduction in 45% after 1 year.[65] However, the impact of weight regain and longer-term outcomes are not available. In PWH, structured exercise with or without dietary intervention reduces abdominal obesity in most studies,[66,67] although data specifically in NAFLD are lacking. One small study reported a lower BMI and higher activity levels in PWH with biopsy-confirmed NAFLD vs controls,[14] and in a multi-ethnic cohort of PWH being screened for hepatic steatosis, nearly half of persons with NAFLD by CAP were nonobese (Lake et al, unpublished data), suggesting that lean NAFLD may play a larger role in PWH than in the general population. In addition, high rates of frailty[68] and sarcopenia in PWH[69] may complicate implementation of traditional diet and exercise recommendations and create a need for pharmacologic options.

Treatment for HIV NAFLD may include careful selection of ART. Although older ART contributed to NAFLD development, contemporary ARTs may be beneficial. A recent study suggested an inverse association between raltegravir (INSTI) use and hepatic steatosis. In this study, PWH (±HCV co-infection) on suppressive efavirenz (a non-NRTI) plus 2 NRTIs for 6 months or more and CAP of 238 or more dB/m were randomized to switch to raltegravir or continue efavirenz, maintaining NRTI backbone. After 48 weeks, CAP scores decreased in the raltegravir group and increased in the efavirenz group, despite similar or greater weight gains in the raltegravir group and a persistent association between higher CAP scores and a higher BMI.[70] Larger studies are needed to clarify relationships between INSTIs and NAFLD regression.

Few NAFLD/NASH treatment trials have included PWH. Because ART is recommended for all PWH, NAFLD interventions must consider concurrent ART administration. Drugs with potentially significant drug–drug interactions require investigations in healthy volunteers before PWH, whereas studies of drugs for which interactions are not expected may proceed.

Tesamorelin, a growth hormone–releasing analog is Food and Drug Administration–approved for the treatment of HIV-associated lipohypertrophy.[71] Obesity and visceral AT are associated with a relative growth hormone deficiency that may contribute to NAFLD. Tesamorelin promotes physiologic release of growth hormone and decreases abdominal adiposity and radiographic liver fat in PWH.[72,73] Its impacts specifically on NAFLD and associated CVD risk currently are being studied (NCT03375788).

For individuals without DM with biopsy-proven NASH, 800 U/d vitamin E for 96 weeks improves NASH histology.[74] In adults with DM, 45 mg/d pioglitazone for 18 months improves NASH histology and may reduce fibrosis.[75] Both treatments have potential adverse effects, including increased risk of prostate cancer with vitamin E, and weight gain, congestive heart failure, and increased bladder cancer risk with pioglitazone.[76] A trial of vitamin E for NASH in PWH currently is underway (NCT03669133). In a small study in persons with HIV and HCV, pioglitazone was well-tolerated and reduced hepatic fat by magnetic resonance spectroscopy (MRS).[77]

Cenicriviroc (CVC), a C-C chemokine–receptor types 2 and 5 antagonist, inhibits HIV entry into target cells. C-C chemokine ligands 2 and 5 are overexpressed in NASH. When CVC was studied as a potential antiretroviral agent, improvement in liver enzyme levels and circulating fibrosis markers were observed.[78] In individuals without HIV, CVC significantly improves fibrosis without impacting steatohepatitis.[79] An ongoing phase 3 trial (NCT03028740) excludes PWH. Because of concurrent anti-HIV activity, CVC should be considered only for NASH therapy in PWH on suppressive ART.

Aramchol (Galmed Pharmaceuticals, Tel Aviv, Israel), a fatty acid–bile conjugate, was studied in 60 patients with biopsy-confirmed NAFLD without HIV,[80] and significantly decreased liver fat by magnetic resonance spectroscopy. In a randomized, placebo-controlled trial comparing the efficacy of 600 mg/d oral Aramchol vs placebo for 12 weeks in 50 PWH with NAFLD as determined by MRI proton density fat fraction,[81] there was no significant reduction in liver fat. Finally, Farnesoid X receptor, peroxisomal proliferator-activated receptor-α/δ, and glucagon-like peptide-1 agonists have shown promise as therapeutics in persons without HIV.[82,83]

The reader is referred to American Association for the Study of Liver Diseases Practice Guidance for the management of patients with NAFLD, which reviews emerging therapies for NASH.[60] In addition, an overview of the current NASH therapeutics landscape in the general population is presented in Table 3. Briefly, diet and exercise remain the mainstay of therapy. Numerous studies of novel therapies are underway, almost none of which are being studied, or have been studied in PWH (with the exception of Aramchol). Further studies are needed to assess the therapeutic efficacy of these emerging agents in PWH who have co-existing NASH and fibrosis.[84]

Clinical Management

Although data on the benefits of screening for NAFLD in PWH are limited, screening individuals with the MetS or increased liver enzyme levels can begin with an abdominal ultrasound. In persons with NAFLD (when other causes of liver disease have been excluded), initial risk stratification may be performed using clinical prediction rules such as FIB-4. Patients with a low FIB-4 (<1.3) may have a low likelihood of advanced fibrosis and may be monitored with a focus on lifestyle interventions.[85] Persons who have high FIB-4 (>2.67) should be referred to a hepatologist for liver disease assessment, and those who are intermediate risk (FIB-4, 1.3–2.67) may undergo further staging with either serum fibrosis markers or elastography. Those with low risk of advanced fibrosis should be advised on lifestyle intervention. Those with moderate-to-high risk of fibrosis should be referred to a hepatologist for consideration of liver biopsy, pharmacotherapy, and clinical trial participation. More specific guidelines for PWH are needed, including ART recommendations, but additional research is needed to inform such guidelines.

Research Priorities

There are significant knowledge gaps in our understanding of HIV NAFLD. Here, we provide a list of priorities addressing unmet needs in the field (Table 4).

Conclusions

NAFLD and NAFLD-related liver and cardiometabolic complications are increasingly prevalent among PWH. However, little is understood about the epidemiology, natural history, pathogenesis, diagnosis, and treatment of this condition in this population. We outlined current knowledge and identified knowledge gaps in HIV-associated NAFLD. Focus on these areas and collaboration between infectious disease and hepatology providers and investigators is essential to decrease the morbidity and mortality associated with NAFLD in PWH.

Funding

Supported in part by the Intramural Research Program of the National Institutes of Health, National Cancer Institute.

Abbreviations used in this paper:

ART	antiretroviral therapy
AT	adipose tissue
BMI	body mass index
CAP	controlled attenuated parameter
CVC	cenicriviroc
CVD	cardiovascular disease
DM	diabetes mellitus
FIB-4	Fibrosis-4
HCV	hepatitis C virus
HIV	human immunodeficiency virus
INSTI	integrase strand transfer inhibitor
IR	insulin resistance
MetS	metabolic syndrome
MRI	magnetic resonance imaging
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NIT	noninvasive tool
NRTI	nucleoside reverse-transcriptase inhibitor
PI	protease inhibitor

PWH persons with human immunodeficiency virus

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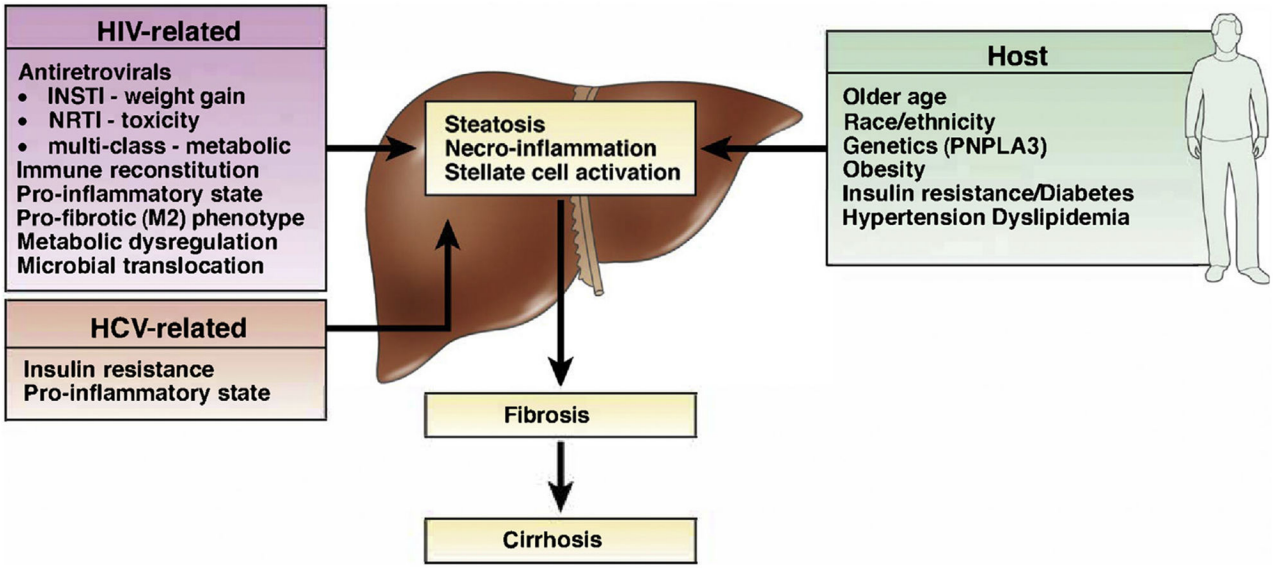

Figure 1.

Nonalcoholic fatty liver disease pathogenesis in persons with human immunodeficiency virus (HIV). HCV, hepatitis C virus; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

Table 1.

NAFLD Epidemiology in People With HIV

Study	Location; design	Participants	NAFLD diagnosis	NAFLD prevalence
Hadigan, 2007	Single-center, US; cross-sectional, prospective, 2004–2006	N = 33; mean age, 46 y; 73% male; 21% HCV+; 85% on ART; HIV duration, 11 y Exclusions: cirrhosis, substance or alcohol use disorder, viral hepatitis treatment, steatogenic medications, type 1 DM, anemia	MRS (intrahepatic triglyceride content, ≥5%)	42%
Guaraldi, 2008	Single-center, Italy; cross-sectional, prospective 2006–2007	N = 225; mean age, 48 y; 72% male; all on ART; HIV duration, 13 y Exclusions: viral hepatitis, substance or excessive alcohol use, autoimmune hepatitis, inborn metabolic disorder	CT scan L/S attenuation ratio, <1.1	37% (44% men, 19% women)
Crum-Cianflone, 2009	Single-center, US; cross-sectional 2006–2007	N = 216; mean age, 40 y; 94% male; 65% on ART; HIV duration, 10 y Exclusions: viral hepatitis, excessive alcohol use	Ultrasound	31%
Rafiq, 2013	NHANES US; retrospective 1998–2008	79 HIV+; 14,606 HIV−HIV+: mean age, 38 y; 76% male Exclusions: viral hepatitis, excessive alcohol use	Men: ALT >40 or AST >37 U/L Women: ALT or AST >31 U/L	HIV+ and HIV− similar (19%)
Sterling, 2013	Single-center, US; cross-sectional 2007–2011	N = 14; mean age, 45 y; 71% male; all on ART Exclusions: viral hepatitis, alcohol abuse, DM; >1 increased liver enzyme level over 6 months	Liver biopsy	65% NAFLD; 26% NASH
Rivero-Juarez, 2013	Multicenter, Spain; prospective, longitudinal 2009–2011	N = 210 (198 completed follow-up evaluation); all without known liver disease and LS <7.2 kPa at baseline Exclusions: viral hepatitis, previous or current ddI, d4T, or hepatotoxic medications; excessive alcohol use	Liver biopsy	11% LS >7.2 kPa over 18 months, 15 unexplained (10 biopsied, all with steatosis)
Nishijima, 2014	Single-center, Japan; cross-sectional, 2004–2013	N = 435; median age, 40 y; 93% male; 52% HIV suppressed; 35% ART-naïve Exclusions: viral hepatitis, excessive alcohol use	Ultrasound	31%
Price, 2014	Multicenter, US; cross-sectional 2010–2013	N = 465 HIV+ (12% HCV+); 254 HIV− (4% HCV+); median age, 53 y; all male; 92% HIV+ on ART Exclusions: excessive alcohol use	CT scan L/S attenuation ratio, <1	13% HIV+ vs 19% HIV−
Morse, 2015	Single-center, US; cross-sectional 2007–2013	N = 62 with 6 months' increased ALT/AST; on ART; median age, 50 y; 94% male; HIV duration, 17.5 y Exclusions: viral hepatitis or chronic liver disease	Liver biopsy	73% NAFLD; 55% NASH
Vuille-Lessard, 2016	Single-center, Canada; cross-sectional 2013–2015	N = 300; mean age, 50 y; 77% male; 90% on ART; HIV duration, 6 y Exclusions: viral hepatitis, excessive alcohol use	Steatosis: CAP ≥238 dB/m; significant fibrosis: TE ≥7.1 kPa	48%; 15% with fibrosis
Lombardi, 2016	Single-center, Greece; period not available	N = 125; mean age, 39.5 y; 91% male; 68% on ART Exclusions: viral hepatitis	Ultrasound and TE fibrosis >7.4 kPa	55%; 18% with fibrosis
Kardashian, 2017	Single-center, US; cross-sectional 2003–2014	N = 121 HIV+, 107 HIV−HIV+ women: mean age, 50 y; 73% on ART; HIV+ men: mean age, 53 y; 97% on ART Exclusions: viral hepatitis, decompensated cirrhosis	MRS (intrahepatic triglyceride content, ≥5%)	17% HIV+ women;33% HIV− women; 41% HIV+ men; 33% HIV− men
Price, 2017	Single-center, US; cross-sectional 2003–2015	N = 122 HIV; 57 HCV; 70 HIV/HCV, 107 HIV−/HCV−; 78% of HIV and 83% of HIV/HCV on ART Exclusions: steatogenic medications, HCV therapy, chronic hepatitis B, decompensated liver disease	MRS (intrahepatic triglyceride content, ≥5%)	28% HIV+; 11% HIV+/HCV+; 19% HCV; 33% HIV−/HCV−

Study	Location; design	Participants	NAFLD diagnosis	NAFLD prevalence
Pembroke, 2017	Single-center, Canada; cross-sectional with longitudinal component 2013–2016	Cross-sectional cohort: N = 726 (23% HCV+, 3% HBV+), median age, 50 y; 75% male, 92% on ART Incidence cohort: >1 TE + CAP measurement and CAP <292 dB/m at baseline Exclusions: other chronic liver diseases, AUDIT-C score ≥7, HCC, liver transplantation, TE failure	Any steatosis: CAP ≥248 dB/m; severe steatosis: CAP ≥292 dB/m; significant fibrosis: TE ≥7.1 kPa	36% steatosis; 29% fibrosis; 42% steatosis progression over a median of 15.4 months; 19% fibrosis progression
Perazzo, 2018	Single-center, Brazil; cross-sectional 2015–2017	N = 395 (367, reliable LSM; 344, reliable CAP); median age, 45 y; 40% male; HIV duration, 10 y Exclusions: viral hepatitis, ART naïve	CAP ≥248 dB/m; liver fibrosis: TE ≥ 8.0 kPa	35%; 9% fibrosis
Torgersen, 2019	Multicenter, US; cross-sectional 2008–2011	171 HIV+ (54% HCV+); 97 HIV− (48% HCV+); HIV+: median age, 54.5 y; 99% male, 91% on ART Exclusions: cardiovascular disease	CT scan L/S attenuation ratio, < 1.0	7.6% (8.2% HIV−)

ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; AUDIT-C, Alcohol Use Disorders Identification Test-Concise; CAP, controlled attenuation parameter; CT, computerized tomography; ddI, didanosine; DM, diabetes mellitus; d4T, stavudine; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; L/S, liver/spleen; LS, liver stiffness; LSM, liver stiffness measurement; MRS, magnetic resonance spectroscopy; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NHANES, National Health and Nutrition Examination Survey; TE, transient elastography.

Table 2.

UROC Values for Noninvasive Test Performance in Persons With HIV

Study	Population	Sample size[a]	Steatosis MRI-PDFF	Steatosis CAP	Steatosis SteatoTest	Fibrosis ≥F2 TE	Fibrosis ≥F3 TE	Fibrosis ≥F4 TE	Fibrosis ≥F2 FibroTest	Fibrosis ≥F2 APRI	Fibrosis ≥F3 APRI	Fibrosis ≥F2 FIB-4	fibrosis ≥F3 FIB-4	Fibrosis ≥F2 ELF	Fibrosis ≥F2 Fibometer	Fibrosis ≥F2 HepaScore	Fibrosis ≥F2 Forns Index[a]	NASH ALT level, >36	NASH NASH Test
emoine et al, 2019	HIV only	49	0.98	0.88	0.68	0.61			0.61	0.86		0.81						0.83	0.6
orse et , 2015	HIV, increased ALT	59				0.93													
chmid, 2015	HIV-HCV	105				0.85		0.97	0.75	0.76		0.77		0.77					
nchaz-onde, 2010	HIV-HCV	100				0.8		0.99											
Kirk et , 2009	HIV-HCV (72%)	192				0.87		0.87											
acoub, 2008	HIV-HCV	272							0.78						0.89	0.84			
Myers, 2003	HIV-HCV	130							0.86										
Macias, 2010	HIV-HCV	519								0.67							0.67		
asteral, 2014	HIV-HCV	116				0.87			0.85	0.73									
erling, 2019	HIV-HCV	108					0.87				0.69		0.66						

TE. SteatoTest and FibroTest (BioPredictive, Paris, France); FibroMeter (EchoSens, Paris, France), HepaScore (Quest Diagnostics, Madison, NJ). ALT, alanine aminotransferase; APRI, AST-to-platelet o index; AUROC, area under the receiver operating characteristic curve; CAP, controlled attenuation parameter; ELF, enhanced liver fibrosis; HCV, hepatitis C virus; HIV, human immunodeficiency s; MRI-PDFF, magnetic resonance imaging proton-derived fat fraction; NASH, nonalcoholic steatohepatitis; TE, transient elastography.

th a liver biopsy comparator

Table 3.

Current and Investigational Therapies for Nonalcoholic Steatohepatitis

Intervention	Mechanism	Target	Data	Experience in HIV	Comment	References
			Current therapies for NASH			
Lifestyle modification	Weight loss by diet and exercise	Decrease hepatic fat content, reduce insulin resistance, modify free fatty acid synthesis	Reversibility of steatohepatitis with exercise; exercise with caloric restriction reduced hepatic steatosis	Widely recognized for role in overall health but underused	Current mainstay of NASH treatment	PMID: 29212576 PMID: 22554085 PMID: 23814606 PMID: 32014512
Bariatric surgery	Surgery	Weight loss	NAFLD prevalence >90% in bariatric surgery patients; NASH resolves in 85% postoperatively	Retrospective review of nationwide database indicates safety and efficacy but underused	Safety not established in NASH; NASH not an indication	PMID: 28714183 PMID: 1733116 PMID: 15826462 PMID: 25917783 PMID: 30157083
Vitamin E	Antioxidant	Free radical scavenger to prevent oxidative stress	Phase 3 RCT: compared with placebo, improvement in NAS; no difference in fibrosis	Small trial illustrating safety and improvement in aminotransferases; larger trials warranted	Utility uncertain; can be used in biopsy-proven NASH; risk of hemorrhagic stroke and prostate cancer	PMID: 20427778 PMID: 28714183 PMID: 21051774 PMID: 2199029 PMID: 31651429
Pioglitazone	Thiazolidinedione insulin sensitizer	Peroxisome proliferator–activated receptor agonist	Phase 3 RCT: nonsignificant improvement in NAS vs placebo	Small studies highlight safety; larger trials warranted	Utility uncertain but can be used in biopsy-proven NASH	PMID: 20427778 PMID: 28714183 PMID: 24334183 PMID: 20959530
Liraglutide	Long-acting glucagon-like peptide (GLP)-1–receptor agonist	Improve glycemic control through pancreatic function	Small phase 2 trial: reduced weight, resolution of steatohepatitis, less progression of fibrosis vs placebo	Case reports of safety and use; several RCTs ongoing	Induces weight loss but notable GI side effects; beneficial CVD effects	PMID: 26608256
Statin	HMG-coA–reductase inhibitors	Reduce cholesterol synthesis	May reduce liver damage in NASH	Safe Studied for lipid-lowering and off-target effects	Deemed safe in NASH, recommended for all high-risk patients	PMID: 25224698 PMID: 30894318 PMID: 25980762
			End points		**Status**	**Trial link**
			Therapies being evaluated in phase 3 RCTs			
Obeticholic acid	Synthetic bile acid derivative	Farnesoid X receptor	Interim analysis: improvement in fibrosis vs placebo	None	Trial ongoing	NCT02548351
Selonsertib	Antifibrotic agent	Apoptosis signal-regulating kinase 1	2 RCTs terminated early for failure to meet primary end point of improved fibrosis	None	Now being studied in combination with other agents	NCT03053050 NCT03053063
Elafibranor	Dual peroxisome proliferator- activated receptor α/Δ agonist	Improve lipid profile and insulin sensitivity	Resolution of NASH; slow progression of fibrosis	None	Trial ongoing	NCT02704403
Cenicriviroc	CCR5/CCR2 chemokine-receptor antagonist	Reduces macrophage trafficking to tissues/ reduces inflammation	Improvement in fibrosis without worsening of NASH	None in NASH; previous safety experience as potential antiretroviral agent	Trial ongoing	NCT03028740

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Intervention	Mechanism	Target	Data	Experience in HIV	Comment	References
Resmetirom	Hepatic thyroid hormone receptor agonist	THR-β	Two-point reduction in NAS and no worsening fibrosis	None	Trial ongoing	NCT03900429
Aramchol	Synthetic fatty acid/bile acid conjugate	Stearoyl coenzyme A desaturase 1	Resolution of NASH without worsening fibrosis	One small trial (NCT0410432) with no benefit to steatosis by MRI-PDFF vs placebo	Trial ongoing	NCT04104321

CCR, C-C chemokine receptor; CVD, cardiovascular disease; GI, gastrointestinal; GLP, glucagon-like peptide; HIV, human immunodeficiency virus; HMG-coA, beta-hydroxy beta-methylglutaryl coenzyme A; MRI-PDFF, magnetic resonance imaging proton-derived fat fraction; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; RCT, randomized controlled trial; THR-β, thyroid hormone receptor-beta.

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Table 4.

Research Priorities in HIV NAFLD

Areas of research	Methods to achieve
Epidemiology, histology, and natural history	
Prevalence of steatosis and fibrosis using advanced imaging	Development of multicenter long-term cohort of HIV NAFLD
Predictors of NASH/fibrosis development, progression and long-term clinical outcomes	Addition of liver imaging and histology to existing cohorts of PWH
Relationship with disease prevalence and progression with other metabolic diseases	
Pathogenesis	
Characterization of differential pathways driving primary vs HIV NAFLD including	Development of multicenter long-term cohort of HIV NAFLD
Contribution of the gut microbiome/microbial translocation	Addition of liver imaging and histology to existing cohorts of PWH
Contribution of HIV viral proteins and products	
Characterization of innate immunologic derangements	
Effect of lipodystrophy on NAFLD development and progression	
Effect of contemporary ART on NAFLD progression	
Noninvasive assessment, treatment, and prevention	
Identification and validation of circulating noninvasive biomarkers	Cross-sectional studies of noninvasive tools in PWH undergoing liver biopsy
Value of current and novel therapies in primary NAFLD in HIV NAFLD	Inclusion of PWH in ongoing NAFLD clinical trials

ART, antiretroviral therapy; HIV, human immunodeficiency virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PWH, people with HIV.