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HIV/AIDS (C YOON, SECTION EDITOR)

Fatty Liver in HIV-Infected Persons

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Abstract
The high efficacy of new antiretroviral regimens has deeply improved survival of patients living with HIV (PLWH), and currently as the population ages, the focus has shifted to comorbidities especially metabolic disorders which includes nonalcoholic fatty liver disease (NAFLD).
Recent Findings Metabolic syndrome is often associated with increased cardiovascular risk that, in turn, is becoming one of the leading causes of death in PLWH. Another important consequence of metabolic syndrome is NAFLD where there is an increasing incidence among PLWH and if progresses could evolve in terminal chronic liver failure. Lipodystrophy, deregulation of the gut-liver axis, and HIV infection itself may contribute simultaneously to NAFLD pathogenesis. Lifestyle modification is the main treatment since no drug has specifically been approved for use in persons with NAFLD, although novel medications and studies are actively being researched.
Summary PLWH have a higher risk for fatty liver disease that is likely due variety risk factors including direct and indirect viral effects, medications, along with the higher prevalence of metabolic syndrome and lipodystrophy.

Keywords NAFLD · HIV · Steatosis · Liver · Dyslipidemia

Introduction

The high efficacy of new antiretroviral regimens adopted for treatment of HIV infection has deeply changed long-term prognosis of patients, ensuring at the same time a better quality of life. For this reason, nowadays, it has been possible to study in this population aging-related events and a number of related comorbidities, most of all those characterized by metabolic disorders. Consequently, viro-immunological efficacy cannot be the only target of modern treatment, but clinicians have to evaluate a number of comorbidities that affect people living with HIV (PLWH), and deal with new emerging diseases. In particular, metabolic alterations are frequent among older PLWH and may be associated with nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) where chronic inflammation due to HIV infection and antiretroviral treatment (ART) may play a role.

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Among PLWH, age-related metabolic alterations, hepatic anatomic and functional changes, altered homeostasis of gastrointestinal microbiota, and anthropometric changes are often associated with the development of insulin resistance and increased cardiovascular risk [1, 2]. HIV infection is associated with fatty liver as a result of multiple viral and host factors. Lipodystrophy, deregulation of the gut-liver axis and HIV infection itself may contribute simultaneously to NAFLD pathogenesis [3]. Although lifestyle changes are the mainstay of treatment, no drug has specifically been approved for use in persons with NAFLD. In this review, we will analyze the literature about the epidemiology, risk factors, and clinical significance of NAFLD in patients with HIV monoinfection.

Definition

The presence of fat in the liver does not automatically mean that liver disease is present and that normal physiologic processes include temporary storage of fat in the liver prior to processing and distribution. Longer-term storage of fat in hepatocytes may lead to increased cell turnover and subsequent development of an immune-mediated response, as well as fibrosis. Simple steatosis is expressed as fatty liver and can

be distinguished from fatty liver disease by the presence of serum transaminase abnormalities or by the development of fibrosis. Fatty liver disease is broadly differentiated by its underlying etiology into alcoholic versus nonalcoholic forms. Alcoholic liver disease (ALD) and NAFLD are histologically similar; therefore, clinical history is necessary to clarify etiology. 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; Hispanic people show higher risk of NAFLD progression [6–10].

Pathogenesis

NAFLD is common among PLWH. There are limited data available on the pathophysiology of NAFLD and the development of fibrosis in this population. The pathogenesis of NAFLD in these patients includes metabolic syndrome, hyperuricemia, HIV-related lipodystrophy, genetic polymorphisms, medications, HIV itself, and the gut microbiome [3]. NAFLD fibrosis stage in HIV monoinfected patients seems to be associated with monocyte activation in the context of obesity, which may be independent of bacterial translocation and gut microbiome [11]. Researchers are studying if HIV infection per se could lead to NAFLD. This process 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 from some of the antiretrovirals, resulting in induced oxidative stress and free fatty acid accumulation [12].

Classically, one of the main metabolic alterations in subjects with HIV infection is the lipodystrophy syndrome. Moreover, HIV may induce a dysregulation of adipogenesis and lipogenesis, decreasing fatty acid oxidation. Another major viral mechanism is the effect of HIV envelope protein gp120 on the hepatic cells that promotes the expression of pro-inflammatory cytokines which activate Kupffer cells and hepatic stellate cells inducing liver fibrosis [13]. In HIV-HCV coinfection there is more rapid progression of liver fibrosis leading cirrhosis and end-stage liver disease. Moreover, HCV is also associated with metabolic alterations such insulin resistance, with genotype 3 HCV being more frequently associated with hepatic steatosis [14]. Antiretroviral regimens play an important role in this context inducing, in particular, insulin resistance, and dyslipidemia. Although a number of commonly used drugs are associated with steatosis, it is not always easy to identify them as causative agents because of the weak temporal relationship between the administration of the drug and the clinical event, the lack of a confirmatory rechallenge, and the high prevalence of NAFLD in HIV patients, which may complicate a proper diagnosis. The scenario is even more complex in PLWH because the various antiretroviral regimens have different effects on liver steatosis. The ritonavir-boosted protease inhibitor (PI/r) use has been associated with several metabolic abnormalities, and NAFLD is becoming a more frequent comorbidity among HIV-infected patients. In a recent study, HIV-infected patients with NAFLD switching from a PI/r to raltegravir showed after 12 months a significantly greater decrease in the degree of hepatic steatosis, as evaluated by controlled attenuation parameter (CAP), in comparison with those with unchanged ART and treated only with lifestyle modification [15]. Another important aspect, particularly debated recently, is weight gain, which seems to be associated with use of the newer integrase inhibitors. On the other hand, excess weight and obesity are frequently evident in women infected with HIV and the prevalence is increasing due to several factors, such as ART, age, gender, and lifestyle [16].

Epidemiology

The real prevalence of NAFLD in patients with HIV is not well understood due to the relative paucity of published studies, but previous results suggest that it ranges from 30 to 50% and progresses at an increased rate compared with the general population [17, 18]. A cross-sectional European study using ultrasound or elastography detected NAFLD and significant liver fibrosis (> F2) in 55% and 18%, respectively, of PLWH, most of whom were young and non-obese [19]. In a case-control study, patients with HIV had more fibrosis by laboratory biomarkers (APRI and FIB-4) and histology when compared with patients without HIV infection despite similar metabolic characteristics [20]. In 62 PLWH with persistently elevated transaminases who underwent liver biopsy, 73% had NAFLD, 55% had NASH, and 16% had bridging fibrosis [21]. A recent meta-analysis of 10 studies enrolling HIV monoinfected patients reported the prevalence of NAFLD (diagnosed via imaging studies), NASH, and fibrosis (diagnosed by biopsy) as 35%, 42% and 22%, respectively [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. found that HIV-infected individuals had a lower prevalence of NAFLD compared with those without HIV [23]. In another study of 122 HIV monoinfected patients, liver fat fraction via magnetic resonance imaging and spectroscopy showed decreased steatosis in HIV women and no difference

in HIV men as compared with HIV negative men and women [24]. The wide variability and the 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.

Fatty Liver Disease in HIV

There are several proposed mechanisms leading to fatty liver disease in PLWH, including the abovementioned traditional risk factors of metabolic syndrome, hyperuricemia, HIV-related lipodystrophy, medications, HIV itself, and the gut microbiome.

Metabolic syndrome has been shown to play a role in the development of fatty liver in PLWH in some studies. In a retrospective study, comparing patients with biopsy-proven NASH with those who did not have NASH, body mass index, waist circumference, and markers of insulin resistance were higher and HDL was lower in those with NASH. Participants with NASH had significantly higher frequency of 2 minor alleles for the PNPLA3 polymorphism ($P < 0.004$) [21]. A cross-sectional study conducted in Italy assessing 225 individuals with HIV infection found that male sex and increased waist circumference were significantly associated ($P < .001$) with NAFLD in a multivariate logistic regression analysis [17]. Fat misdistribution in the setting of HIV also known as HIV-related lipodystrophy occurs more frequently in those with long-standing infection [25].

Lipodystrophy is thought more to be a sequelae of ART rather than HIV itself and has long-term cardiovascular implications, as it is associated with insulin resistance and dyslipidemia [26, 27]. Risk factors for lipodystrophy include older age, use of nucleoside analogue reverse transcriptase inhibitors (nRTIs) and protease inhibitors (PIs), and total duration of ART [26]. Increased visceral adiposity has been linked to worsening insulin resistance: Studies have in fact demonstrated that PLWH with lipodystrophy had higher hepatic fat content ($P < 0.05$) [28]. The role of certain ART in fatty liver continues to be investigated. It has been proposed that nRTIs can cause hepatic microvesicular steatosis by causing inhibition of mitochondrial DNA replication and overexpression of the sterol regulatory binding protein. nRTIs also cause hypertriglyceridemia, lipodystrophy, and hypoadiponectinemia [23]. Plasma adiponectin is an adipose-specific protein with putative anti-atherogenic and anti-inflammatory effects associated with insulin resistance. Additionally, the ritonavir-boosted protease inhibitor (PI/r) use has been associated with several metabolic abnormalities, insulin resistance, and dyslipidemia and NAFLD is becoming a very frequent comorbidity among PLWH [29, 30]. In an observational, prospective study of patients with NAFLD, the change in amount of liver steatosis after switch from PI/r to integrase inhibitors was analyzed. Authors enrolled 61 patients receiving a PI/r plus two nucleoside analogues, who either switched from the PI/r to raltegravir or were maintained on current ART with lifestyle modification. After 12 months, patients switched from a PI/r to raltegravir showed a significantly greater decrease in the degree of hepatic steatosis compared with those with unchanged cART and treated only with lifestyle modification [31].

Longer cumulative ART exposure, nRTI exposure duration, lamivudine exposure, and dideoxynucleoside exposure were all significantly associated with fatty liver in a univariate analysis in the MACS [23]. Conversely, a smaller study of 65 individuals with HIV infection found that neither NASH nor fibrosis was associated with duration of ART or specific antiretroviral drugs [21]. Overall, the association between ART and fatty liver is likely driven by the adverse metabolic effects of ART, separate from the direct drug toxicity and hypersensitivity that can occur [32]. Conflicting reports of ART exposure and fatty liver remain, such as the role of HIV infection in causing fatty liver. There is increasing evidence of the role of the gut microbiome on fatty liver disease. When gut integrity is compromised, the increase of markers of bacterial translocation such as lipopolysaccharide (LPS) is observed. LPS is a component of the cell walls of gram-negative bacteria. These heightened levels of LPS can lead to a state of dysregulated immune activation through a cascade of cytokine production which may affect HIV disease progression response to therapy and AIDS comorbidities due to increased microbial translocation [33]. HIV-associated microbial translocation occurs because in the setting of acute and even chronic infection, CD4+ cell depletion is more prevalent in the gut mucosa versus peripheral blood and lymph nodes, thereby leading to endothelial damage and exhaustion of intestinal macrophages. Subsequently, increased levels of LPS activate Kupffer cells, leading to release of pro fibrotic and pro inflammatory cytokines.

Diagnosis

There is not a standardized noninvasive method to make a reliable diagnosis of NAFLD in PLWH. However clinicians can evaluate NAFLD using ultrasound, elastography, and non-elastographic techniques. In a recent study, liver steatosis was evaluated by a commercially available elastography device with the standard M probe, leading to the measurement of CAP and liver stiffness. Elastography examinations were conducted by an experienced operator and were considered as valid if at least 10 successful measurements could be achieved, with an interquartile range < 30% of the median liver stiffness value and a success rate > 60% [34]. Diagnosis of NAFLD was made by a CAP value ≥ 238 dB/m, indicative of the presence of significant hepatic steatosis

(involving ≥ 10% of hepatocytes). Diagnosis of moderate-to-severe hepatic steatosis was made by a CAP value ≥ 260 dB/m [31, 35].

Treatment

Lifestyle modifications are the keystone to treatment of fatty liver disease, as there are limited pharmacologic therapies for NAFLD. A separate meta-analysis showed improvement in hepatic fat with exercise in the absence of weight loss [36]. Many of the currently available pharmacologic therapies for fatty liver disease, at present, have not been studied in PLWH. In nondiabetic persons, vitamin E, 800 units daily, led to notable improvement in NASH histology but not fibrosis. Use of pioglitazone, a thiazolidinedione, showed good results in steatosis, lobular inflammation, and the NAFLD Activity Score but did not achieve improvement or resolution of NASH and did not modify fibrosis [37]. Currently, vitamin E and pioglitazone are the mainstay of pharmacologic treatments for select persons with NASH. In a recent study, authors have evaluated the efficacy of Vitamin E in the treatment of NASH in the PLWH population [38]. They enrolled 27 patients with HIV infection associated to NASH who have been treated with 800 IU daily of oral Vitamin E for 24 weeks. Compared with baseline, 24 weeks of vitamin E treatment improved ALT, CAP, scores and CK-18. Conversely, there was no change in BMI. No serious adverse event was reported, and no patient was lost to follow-up. Researchers concluded that vitamin E may be an effective and well-tolerated treatment for NASH in HIV-infected patients. Therapies for NAFLD include peroxisome proliferator-activated receptor (PPAR) agonists; stearoyl-CoA desaturase (SCD) inhibitors; incretin-based agonists, such as glucagon-like peptide (GLP) agonists; tumor necrosis factor alpha inhibitors; those that target the gut microbiome; and most importantly, antifibrotic agents [39]. To avoid fibrosis that is related to long-term mortality in NAFLD, researchers have tested many antifibrotic agents in clinical trials: Simtuzumab, a monoclonal antibody directed against lysyl oxidase-like2 (LOXL2) enzyme, was studied in persons with HIV or HCV infection or HIV/HCV coinfection in the setting of advanced liver disease without significant efficacy [40]. Other studies have found altered levels of chemokine, involved in leukocyte chemotaxis and fibrosis, in persons with NASH [41]. A study evaluating 2 distinct cohorts proved that blockade of CCR5 leads to improvement in hepatic fibrosis [42]. Our recent study has evaluated the in vitro effects of treatment with Maraviroc, a CCR5 inhibitor on a human hepatic stellate cell line in patients with HIV/HCV coinfection. It analyzed the effect of Maraviroc on LX-2, a human hepatic stellate cell line (HSC). Treatment with Maraviroc resulted in a block in S phase of LX-2 cells with increased expression levels of cyclin D1 and p21 while the expression of p53 was reduced. Maraviroc was also able to block the accumulation of fibrillar collagens and extracellular matrix proteins (ECM), as demonstrated by the decrease of specific markers as collagen type I, α-SMA, and TGF-β1. In addition we observed a downregulation of both metalloproteins (MMP-2, MMP-9), used for the degradation of the extracellular matrix and their inhibitors (TIMP-1, TIMP-2). The identification of a compound that may modulate the dynamic of liver fibrosis could be crucial in all chronic liver diseases. Maraviroc could play an important role because, in addition to its own anti-HIV activity, it could reduce the release of pro-inflammatory cytokines implicated in liver fibrogenesis [43]. Another possible treatment of NAFLD is based on tesamorelin, a growth hormone-releasing hormone (GHRH) analogue initially approved for treatment of HIV-related lipodystrophy was found to improve serum ALT levels and steatosis on magnetic resonance spectroscopy [44, 45]. A multicenter study, to further investigate these preliminary results, has been performed in the USA: This randomized, double-blind, multicenter study versus placebo enrolled PLWH with hepatic fat diagnosed by proton magnetic resonance spectroscopy. Participants were randomly assigned (1:1) to receive either tesamorelin 2 mg once daily or placebo once daily for 12 months, followed by a 6-month open-label phase in which all participants received only tesamorelin 2 mg daily. Sixty-one patients were enrolled; of whom, 30 were treated by tesamorelin and 30 received placebo. Patients receiving tesamorelin had a greater reduction of hepatic fat fraction (HFF) than did patients receiving placebo. After 12 months, 35% of individuals receiving tesamorelin and 4% receiving placebo had a HFF of less than 5% ($p = 0{\cdot}0069$). Tesamorelin might be beneficial in PLWH and NAFLD. Further studies are needed to determine the long-term effects of tesamorelin on liver histology [46].

Several drugs are at present in phase II and III clinical trials, which specifically target NAFLD in HIV, including CC chemokine receptor 5 inhibitors, growth hormone-releasing factor agonists, and stearoyl-CoA desaturase inhibitors.

Conclusions

In conclusion, in the actual scenario of management of HIV, clinicians should consider monitoring of metabolic disorders and prevention of NAFLD. PLWH should be screened for NAFLD and counseled for risk factor modification and lifestyle changes. This condition may in fact lead to liver decompensation and increase cardiovascular risk. This is important above all for patents with HIV infection at higher risk of NAFLD for evidence of long history of antiretroviral treatment, metabolic syndrome, aging, and related comorbidities. Although the life expectancy of HIV-infected patients has increased dramatically after the introduction of cART, liver-

related morbidity continues to be a great problem in this population. In some patients, residual inflammation persists and when it is associated to metabolic disorders may increase the risk of NAFLD and other comorbidities in a dangerous continuous circle in which every factor sustains and makes worse the other one. These developments should make us aware of the high risk of NAFLD in this population and warrant further research on modification of both the traditional and HIV-related risk factors and therapeutic interventions. [47]

References

1. Guaraldi G, Lonardo A, Maia L, Palella FJ Jr. Metabolic concerns in aging HIV-infected persons: from serum lipid phenotype to fatty liver. AIDS. 2017;31(Suppl 2):S147–56. https://doi.org/10.1097/QAD.0000000000001483.
2. Crum-Cianflone N, Krause D, Wessman D, Medina S, Stepenosky J, Brandt C, et al. Fatty liver disease is associated with underlying cardiovascular disease in HIV-infected persons(*). HIV Med. 2011;12(8):463–71. https://doi.org/10.1111/j.1468-1293.2010.00904.x.
3. Morrison M, Hughes HY, Naggie S, Syn WK. Nonalcoholic fatty liver disease among individuals with HIVmono-infection: A growing concern? Dig Dis Sci. 2019;64(12):3394–401. https://doi.org/10.1007/s10620-019-05861-7.
4. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology. 2005;129:113–21.
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 nonalcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34:274–85.
7. Williams CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, 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;140:124–31.
8. Marchesini G, Babini M. Nonalcoholic fatty liver disease and the metabolic syndrome. Minerva Cardioangiol. 2006;54:229–39.
9. Pagano G, Pacini G, Musso G, Gambino R, Mecca F, Depetris N, et al. Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association. Hepatology (Baltimore, MD). 2002;35:367–72.
10. Armstrong MJ, Adams LA, Canbay A, Syn WK. Extrahepatic complications of nonalcoholic fatty liver disease. Hepatology. 2014;59:1174–97.
11. Maurice JB, Garvey L, Tsochatzis EA, Wiltshire M, Cooke G, Guppy N, et al. Monocyte-macrophage activation is associated with non alcoholic fatty liver disease and liver fibrosis in HIV monoinfection independently of the gut microbiome and bacterial translocation. AIDS. 2019;33(5):805–14. https://doi.org/10.1097/QAD.0000000000002133.
12. Debes JD, Bohjanen PR, Boonstra A. Mechanisms of accelerated liver fibrosis progression during HIV infection. J Clin Transl Hepatol. 2016;4:328–35.
13. Bruno R, Galastri S, Sacchi P, Cima S, Caligiuri A, DeFranco R, et al. gp120 modulates the biology of human hepatic stellate cells: a link between HIV infection and liver fibrogenesis. Gut. 2010;59(4):513–20.
14. Woreta TA, Sutcliffe CG, Mehta SH, Brown TT, Higgins Y, Thomas DL, et al. Incidence and risk factors for steatosis progression in adults coinfected with HIV and hepatitis C virus. Gastroenterology. 2011;140(3):809–17.
15. Coronel-Castillo CE, Qi X, Contreras-Carmona J, Ramírez Pérez OL, Méndez-Sánchez N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in HIV infection: a metabolic approach of an infectious disease. Expert Rev Gastroenterol Hepatol. 2019;13(6):531–40. https://doi.org/10.1080/17474124.2019.1599284.
16. Lake JE, Wu K, Bares SH, Debroy P, Godfrey C, Koethe JR, et al. Clin Infect Dis. 2020:ciaa177. https://doi.org/10.1093/cid/ciaa177.
17. Guaraldi G, Squillace N, Stentarelli C, Orlando G, D'Amico R, Ligabue G, et al. Nonalcoholic fatty liver disease in HIV-infected patients referred to a metabolic clinic: prevalence, characteristics, and predictors. Clin Infect Dis. 2008;47:250–7.
18. Crum-Cianflone N, Dilay A, Collins G, Asher D, Campin R, Medina S, et al. Nonalcoholic fatty liver disease among HIV-infected persons. J Acquir Immune Defic Syndr (1999). 2009;50:464–73.
19. Lombardi R, Sambatakou H, Mariolis I, Cokkinos D, Papatheodoridis GV, Tsochatzis EA. Prevalence and predictors of liver steatosis and fibrosis in unselected patients with HIV monoinfection. Dig Liver Dis. 2016;48:1471–7.
20. Vodkin I, Valasek MA, Bettencourt R, Cachay E, Loomba R. Clinical, biochemical and histological differences between HIVassociated NAFLD and primary NAFLD: a case-control study. Aliment Pharmacol Ther. 2015;41:368–78.
21. Morse CG, McLaughlin M, Matthews L, Proschan M, Thomas F, Gharib AM, et al. Nonalcoholic steatohepatitis and hepatic fibrosis in HIV-1-monoinfected adults with elevated aminotransferase levels on antiretroviral therapy. Clin Infect Dis. 2015;60:1569–78.
22. Maurice JB, Patel A, Scott AJ, Patel K, Thursz M, Lemoine M. Prevalence and risk factors of nonalcoholic fatty liver disease in HIV-monoinfection. AIDS (London, England). 2017;31:1621–32.
23. Price JC, Seaberg EC, Latanich R, Budoff MJ, Kingsley LA, Palella FJ Jr, 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, Price JC, Sarkar M, Korn N, et al. Sex differences in the association of HIV infection with hepatic steatosis. AIDS (London, England). 2017;31:365–73.
25. Lichtenstein KA, Ward DJ, Moorman AC, Delaney KM, Young B, Palella FJ Jr, et al. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. AIDS. 2001;15:1389–98.
26. Carr A. HIV lipodystrophy: risk factors, pathogenesis, diagnosis and management. AIDS. 2003;17(Suppl 1):S141–8.
27. Lana LG, Junqueira DR, Perini E, de Menezes PC. Lipodystrophy among patients with HIV infection on antiretroviral therapy: a systematic review protocol. BMJ Open. 2014;4(3):e004088.
28. Sutinen J, Häkkinen AM, Westerbacka J, Seppälä-Lindroos A, Vehkavaara S, Halavaara J, et al. Increased fat accumulation in the liver in HIV-infected patients with antiretroviral therapy associated lipodystrophy. AIDS. 2002;16(16):2183–93.
29. Vallet-Pichard A, Mallet V, Pol S. Nonalcoholic fatty liver disease and HIV infection. Semin Liver Dis. 2012;32(2):158–66.
30. Gervasoni C, Cattaneo D, Filice C, Galli M, Gruppo Italiano Studio-NASH in malattie infettive. Drug-induced liver steatosis in patients with HIV infection. Pharmacol Res. 2019;145:104267. https://doi.org/10.1016/j.phrs.2019.104267.
31. Calza L, Colangeli V, Borderi M, Coladonato S, Tazza B, Fornaro G, et al. Improvement in liver steatosis after the switch from a ritonavir-boosted protease inhibitor to raltegravir in HIV-infected patients with non-alcoholic fatty liver disease. Infect Dis (Lond).

2019;51(8):593–601. https://doi.org/10.1080/23744235.2019.1629008.
32. Price JC, Thio CL. Liver disease in the HIV-infected individual. Clin Gastroenterol Hepatol. 2010;8(12):1002–12.
33. Marchetti G, Tincati C, Silvestri G. Microbial translocation in the pathogenesis of HIV infection and AIDS. Clin Microbiol Rev. 2013;26(1):2–18.
34. Sasso M, Beaugrand M, de Ledinghen V, Douvin C, Marcellin P, Poupon R, et al. Controlled attenuation parameter (CAP): a novel VCTE guided 600 ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes. Ultrasound Med Biol. 2010;36:1825–35.
35. Paul J, Venugopal RV, Peter L, Shetty KNK, Shetti MP. Measurement of controlled attenuation parameter: a surrogate marker of hepatic steatosis in patients of nonalcoholic fatty liver disease on lifestyle modification – a prospective follow-up study. Arq Gastroenterol. 2018;55:7–13.
36. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology. 2015;149(2):367–78.e5; quiz e14–5. https://doi.org/10.1053/j.gastro.2015.04.005.
37. Armstrong MJ, Houlihan DD, Rowe IA. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010;363(12):1185; author reply 1186. https://doi.org/10.1056/NEJMc1006581.
38. Sebastiani G, Saeed S, Lebouche B, de Pokomandy A, Szabo J, Haraoui LP, et al. Vitamin E Is an effective treatment for nonalcoholic steatohepatitis in HIV mono-infected patients. AIDS. 2020;34(2):237–44. https://doi.org/10.1097/QAD.0000000000002412.
39. Oseini AM, Sanyal AJ. Therapies in nonalcoholic steatohepatitis (NASH). Liver Int. 2017;37(Suppl 1):97–103.
40. Meissner EG, McLaughlin M, Matthews L, Gharib AM, Wood BJ, Levy E, et al. Simtuzumab treatment of advanced liver fibrosis in HIV and HCV-infected adults: results of a 6-month open-label safety trial. Liver Int. 2016;36(12):1783–92. https://doi.org/10.1111/liv.13177.
41. Bertola A, Bonnafous S, Anty R, Patouraux S, Saint-Paul MC, Iannelli A, et al. Hepatic expression patterns of inflammatory and immune response genes associated with obesity and NASH in morbidly obese patients. PLoS One. 2010;5(10):e13577. https://doi.org/10.1371/journal.pone.0013577.
42. Sherman KE, Abdel-Hameed E, Rouster SD, Shata MTM, Blackard JT, Safaie P, et al. Improvement in hepatic fibrosis biomarkers associated with chemokine receptor inactivation through mutation or therapeutic blockade. Clin Infect Dis. 2019;68(11):1911–8. https://doi.org/10.1093/cid/ciy807.
43. Coppola N, Perna A, Lucariello A, Martini S, Macera M, Carleo MA, et al. Effects of treatment with Maraviroc a CCR5 inhibitor on a human hepatic stellate cell line. J Cell Physiol. 2018;233(8):6224–31. https://doi.org/10.1002/jcp.26485.
44. Stanley TL, Feldpausch MN, Oh J, Branch KL, Lee H, Torriani M, et al. Effect of tesamorelin on visceral fat and liver fat in HIV-infected patients with abdominal fat accumulation: a randomized clinical trial. JAMA. 2014;312(4):380–9.
45. Seth A, Sherman KE. Fatty liver disease in persons with HIV infection. Top Antivir Med. 2019;27(2):75–82.
46. Stanley TL, Fourman LT, Feldpausch MN, Purdy J, Zheng I, Pan CS, et al. Effects of tesamorelin on non-alcoholic fatty liver disease in HIV: a randomised, double-blind, multicentre trial. Lancet HIV. 2019;6(12):e821–30. https://doi.org/10.1016/S2352-3018(19)30338-8.
47. Van Welzen BJ, Mudrikova T, El Idrissi A, Hoepelman AIM, Arends JE. A Review of Non-Alcoholic Fatty Liver Disease in HIVInfected Patients: The Next Big Thing? Infect Dis Ther. 2019;8(1):33–50. https://doi.org/10.1007/s40121-018-0229-7.