Current HIV/AIDS Reports (2020) 17:601–614
https://doi.org/10.1007/s11904-020-00531-0

CO-INFECTIONS AND COMORBIDITY (S NAGGIE, SECTION EDITOR)

NASH in HIV

Adriana Cervo[1,2] · Mohamed Shengir[3] · Keyur Patel[4] · Giada Sebastiani[5]

Published online: 28 September 2020

Abstract

Purpose of Review Aging-related comorbidities, including liver disease, represent the main drivers of morbidity and mortality in people with HIV (PWH). Nonalcoholic fatty liver disease (NAFLD) seems a frequent comorbidity in aging PWH nowadays. NAFLD results from a fat deposition into the liver parenchyma that may evolve to nonalcoholic steatohepatitis (NASH), a state of hepatocellular inflammation and injury in response to the accumulated fat leading to liver fibrosis and cirrhosis. We here review the current status of knowledge regarding this emerging comorbidity in PWH.

Recent Findings Recent studies suggest that PWH are at higher risk for both NASH and NASH-related liver fibrosis. Several hypothesized pathogenic mechanisms may account for this finding, including increased metabolic comorbidities, hepatotoxic effect of lifelong antiretroviral therapy, and chronic HIV infection. In clinical practice, non-invasive diagnostic tests, such as serum biomarkers and elastography, may help identify patients with NASH-related fibrosis, thus improving risk stratification, and enhancing clinical management decisions, including early initiation of interventions such as lifestyle changes and potential pharmacologic interventions.

Summary Clinicians should remain informed of the frequency, significance, and diagnostic and management approach to NASH in PWH.

Keywords Nonalcoholic steatohepatitis · Liver fibrosis · Metabolic comorbidities · Antiretroviral therapy · Non-invasive diagnostic tests · Interventions

Introduction

HIV continues to be a major global public health issue. In 2018, there were approximately 37.9 million people with HIV (PWH) worldwide [1]. The advent of combination antiretroviral therapy (ART) has considerably improved the health of PWH: in 2018, 50% of PWH in North America were predicted to be over 50 years old [2]. As a consequence, the focus in the management of PWH is shifting to chronic non-infectious comorbidities as both chronic HIV infection itself and long-term ART may affect the trajectory of aging-related conditions [3–5]. Nowadays, mortality from liver disease is higher than that from cardiovascular diseases and second only to AIDS-related mortality [6]. Over the last decade, the proportion of deaths attributed to liver-related causes has increased between 8 and 10-fold in the post-ART era while AIDS-related mortality has fallen more than 90-fold [7–9]. While co-infection with hepatitis B (HBV) and C (HCV) viruses is believed to have driven this trend in the past, risk factors unique to this population, combined with frequent metabolic comorbidities, may contribute to nonalcoholic fatty liver disease (NAFLD) in HIV mono-infected patients, who represent 86–89% of PWH [10•].

This article is part of the Topical Collection on *Co-infections and Comorbidity*

✉ Giada Sebastiani
giada.sebastiani@mcgill.ca

1 Division of Infectious Diseases, Chronic Viral Illness Service, McGill University Health Centre, Montreal, Canada

2 Department of Health Promotion Sciences and Mother and Child Care "Giuseppe D'Alessandro", University of Palermo, Palermo, Italy

3 Division of Experimental Medicine, McGill University, Montreal, Canada

4 Division of Gastroenterology, University Health Network Toronto, Toronto General Hospital, Toronto, Canada

5 Division of Gastroenterology and Hepatology, Chronic Viral Illness Service Royal Victoria Hospital, McGill University Health Centre, 1001 Blvd. Décarie, Montreal QC H4A 3J1, Canada

Definition of NAFLD

The World Health Organization has called for a cessation in further growth in obesity and diabetes prevalence, with a goal to reduce by one-third premature mortality from non-communicable disease by 2030 [11]. Diabetes and obesity represent the main risk factors for NAFLD, the commonest liver disease globally, affecting 25% of the general population [12–15]. NAFLD is an umbrella term that encompasses a spectrum of clinical and pathologic features characterized by a fatty overload involving over 5% of the liver weight in the absence of other causes of liver disease. Nonalcoholic fatty liver (NAFL) or simple steatosis can evolve to nonalcoholic steatohepatitis (NASH), significant scarring (fibrosis), and liver cirrhosis, eventually resulting in end-stage complications, such as liver failure and hepatocellular carcinoma (HCC) [15, 16]. In the last three decades, the burden of liver cirrhosis in the general population is rapidly increasing, resulting in significant health and economic consequences [17]. NASH has played a central role in contributing to this burden in the general population: it is now the second leading indication for liver transplant in North America, and is projected to become the main indication in the next 10 years [18, 19]. NASH represents the progressive counterpart of NAFLD, defined as presence of hepatic steatosis and necroinflammatory histologic changes. In the general population, around one-third of patients with NAFLD have NASH, corresponding to an estimated global prevalence of 6–7% [20]. Despite advances in non-invasive diagnostic tests in liver disease, liver biopsy remains the gold standard to differentiate NASH from simple hepatic steatosis since no accurate biomarker, able to predict histologic components required to diagnose NASH, has been identified so far. The most frequently used histologic classification adopted for the diagnosis and staging of NASH is the NAFLD activity score (NAS). The diagnosis is based on three components (steatosis, score 0–3; lobular inflammation, score 0–3; hepatocyte ballooning, score 0–2), with a cumulative NAS score $\geq$ 5 considered diagnostic for NASH [21]. Liver fibrosis is evaluated separately from NAS and has been classified into 5 stages, from no/minimal fibrosis to cirrhosis. Stage $\geq$ 2 liver fibrosis, which is also defined as significant liver fibrosis, is a threshold that indicates a progressive liver disease which will eventually lead to cirrhosis and end-stage complications [22]. Alternate scoring systems such Steatosis Activity Fibrosis (SAF) score have also been proposed for clinical practice, but have not been readily adopted by histopathologists outside European centers [23].

Epidemiology of NAFLD and NASH in HIV

The prevalence of NAFLD among PWH ranges from 13 to 65%, with a recent meta-analysis indicating this as being 35% [24–30]. Despite this range in prevalence, likely attributable to differences in study population and diagnostic tools, NAFLD seems to be a more frequent clinical entity in PWH compared with the general population. Moreover, several studies reported an increased severity of liver disease, as indicated by higher prevalence of significant liver fibrosis and cirrhosis (Table 1). A case–control study found that, compared with age and sex-matched HIV-negative NAFLD, patients with HIV-associated NAFLD had significantly higher rates of steatohepatitis (37% versus 63%), and more features of hepatocyte injury, including lobular inflammation and acidophil bodies [36•]. Few histologic studies are available to determine the prevalence of NASH in HIV mono-infected patients. In many of these studies, patients with elevated alanine aminotransferase (ALT) underwent histologic assessment, thus introducing a selection bias [34]. In a study of 55 patients with elevated ALT and available liver biopsy, Crum-Cianflone et al. found a prevalence of NASH at 7.3% [32]. Similarly, a study from the UK including 97 HIV mono-infected patients reported a prevalence of 8.2% [39]. Conversely, some studies which included patients with persistently elevated ALT found a much higher prevalence of NASH, ranging from 53.3 to 63.6% [31, 33, 35, 36]. The pooled prevalence of NASH reported by Maurice et al. was 41.7% [24••]. As shown in Table 1, it is likely that the characteristics of the study population play a main role in dictating the reported prevalence figures. These include proportion of elevated ALT, sex, and ethnicity, as well as frequency of metabolic comorbidities and HIV characteristics, particularly type and duration of ART exposure, as well as duration and control of HIV infection. A Canadian study from our team used the serum biomarker cytokeratin 18 to screen PWH for NASH [42]. Cytokeratin 18 is a biomarker of hepatocyte apoptosis, which occurs in NASH but not in NAFL, and has been shown good accuracy for NASH [43]. When applied to 202 consecutive HIV mono-infected patients, the prevalence of NASH was at 11.4%, and it was confirmed in all cases with available liver histology. There are very few longitudinal studies investigating the incidence of NAFLD and the progression of liver fibrosis in HIV-infected patients (Table 2). Despite the short-term follow-up, the progression of both hepatic steatosis and liver fibrosis appears significant in this population, with higher rate in HIV-HCV co-infected patients [44–47].

Pathogenesis of NASH in the Context of HIV Infection

Classic Pathogenic Factors

The pathogenesis of NASH in PWH is a complex intersection between extremely frequent classical pathogenetic factors and unique risk factors linked to HIV infection. In HIV-negative

Table 1 Prevalence of NAFLD/NASH and significant liver fibrosis in HIV mono-infected patients

	Design/country	Sample	Diagnostic method	Age (years)	Males (%)	Alcohol excess (%)	BMI (Kg/m^2)
Lemoine [31]	Prospective/France 2006	14	Liver biopsy	43.5 (range 31–58)	86	0	23.0 ± 3.4
Guaraldi [25]	Prospective/Italy 2008	255	CT scan	48 (range 19–74)	72.4	0	23.7 ± 3.4
Crum-Cianflone [32]	Prospective/USA 2010	216 (biopsy $n = 55$)	US (liver biopsy in a subgroup)	41 (IQR 30–46)	96.2	12.5	26.0 ± 4.1
Ingiliz [33]	Prospective/France 2009	30	Liver biopsy	46 (range 31–67)	97	0	23.0 ± 3.1
Sterling [34]	Prospective/USA 2013	14	Liver biopsy	45 ± 10	71	0	29.9 ± 7.4
Nishijima [26]	Prospective/Japan 2014	435	US	10 (range 35–50)	93	0	22.1 (IQR 20.2–24.9)
Macias [27]	Prospective/Spain 2014	505	CAP	46 (IQR 41–49)	69	11	23.2 (IQR 20.9–26)
Morse [35]	Prospective/USA 2015	62	Liver biopsy	50 (range 17–67)	94	0	27.6 (range 15.3–47.1)
Vodkin [36]	Prospective/USA 2015	33	Liver biopsy	44.8 ± 9.8	78.8	0	29.8 ± 6.0
Lui [28]	Prospective/China 2016	80	H-MRS/CK-18/TE	53.9 ± 11.2	92.5	1	23.6 ± 3.9
Vuille-Lessard [37]	Prospective/Canada 2016	300	CAP/TE	50	43.3	0	NA
Lombardi [38]	Retrospective/UK 2016	125	US/TE	39.6 ± 10.3	91	6.5	24.6 ± 2.9
Lombardi [29]	Retrospective/UK 2017	20 (out of 156)	Liver biopsy	47.5 ± 8.5	91.7	0	NA
Price [30]	Prospective/USA 2017	122	H-MRS	51 (IQR 47–57)	53	14	26 (IQR 24–30)
Prat [39]	Retrospective/UK 2018	97	Liver biopsy	47 ± 10	93	20	27 ± 6
Mohr [40]	Prospective/Germany 2018	289	CAP/TE	45 (IQR 20–75)	78	NA	24 (range 16–41)
Perazzo [41]	Prospective/Brazil 2018	395	CAP/TE	45 (IQR 35–52)	40	23	25.7 (IQR 23.2–29.4)
Benmassaoud [42]	Prospective /Canada 2018	202	CAP/TE, CK-18	53.8 ± 10.5	77.7	0	NA

	Diabetes (%)	ALT elevation (%)	Duration HIV infection (years)	Time on ART (years)	NAFLD/NASH (%)	≥F2 Fibrosis /cirrhosis (%)	NAFLD predictors
Lemoine [31]	NA	100	10.6 (median)	NA	57.1/57.1	28.6	NA
Guaraldi [25]	12.2	28	12.3 ± 5.0	NA	36.9/NA	NA	AST/ALT ratio, male sex, waist circumference, NRTI exposure
Crum-Cianflone [32]	5.1	100	14 (IQR 6–20)	NA	31/7.3	3.6	NA
Ingiliz [33]	NA	100	13 (IQR 9–15)	NA	60/53.3	20	NASH: ↑TG, hyperglycemia, HOMA-IR
Sterling [34]	0	100	NA	NA	64.3/28.6	14.3	NAFLD: ↑GGT NASH: HOMA-IR
Nishijima [26]	5.1	NA	NA	1.4 (IQR 0–5.6)	31/NA	NA	BMI, dyslipidaemia, AST/ALT ratio
Macias [27]	4.4	NA	NA	NA	40/NA	NA	BMI
Morse [35]	9.7	100	17.5 (range 2.3–27.8)	12.9 (range 1.7–22.8)	72.6/54.8	19.4	NASH: obesity, insulin resistance, PNPLA3
Vodkin [36]	18.2	NA	NA	NA	100/63.6	33.3/6	NASH: HIV duration
Lui [28]	48.8	NA	8 (IQR 4–13)	NA	28.7/NA	13.8/5	↑TG
Vuille-Lessard [37]	11.3	NA	NA	NA	48/NA	15/2.3	BMI, ↑ALT
Lombardi [38]	5.6	16.8	6 (IQR 0–26)	3 (IQR0–17)	55/NA	17.6/NA	Male sex, age, HOMA-IR, GGT
Lombardi [29]	11	100	14 (IQR 2–30)	11 (IQR 0–26)	65/NA	NA/5	NA
Price [30]	8.2	NA	NA	7.9 (IQR 3.3–12.5)	28/NA	NA/2.5	HIV RNA, HOMA-IR

Table 1 (continued)

Prat [39]	11	100	10.5 ± 9.3	8.3 ± 7.2	28.7/8.2	20	NA
Mohr [40]	4	NA	8 (range 0–29)	6 (0–23)	40.8/NA	NA	BMI, hemoglobin glycosylated, TG
Perazzo [41]	10	3	10 (6–16)	7 (4–14)	35/NA	9/4.9	Central obesity, diabetes, dyslipidemia, metabolic syndrome
Benmassaoud [42]	13.4	75	NA	NA	53.9/11.4	10.9/4.5	NASH: HOMA-IR, ↑ALT

Continuous variables are expressed as mean ± standard deviation or median (interquartile range or range) and categorical variables are presented as percentages. Significant liver fibrosis is defined as stage ≥F2 or equivalent

ALT alanine aminotransferase; *ART* antiretroviral therapy; *BMI* body mass index; *CAP* controlled attenuation parameter; *CK-18* cytokeratin 18; *CT* computed tomography; *HIV* human immunodeficiency virus; *IQR* interquartile range; *GGT* gamma glutamyl transferase; *H-MRS* proton magnetic resonance spectroscopy; *HOMA-IR* homeostatic model assessment of insulin resistance; *NA* not available; *NAFLD* nonalcoholic fatty liver disease; *NASH* nonalcoholic steatohepatitis; *NRTI* nucleoside reversal transcriptase inhibitors; *PNPLA3* patatin-like phospholipase domain-containing protein 3; *TE* transient elastography; *TG* triglycerides; *US* ultrasound

NASH, insulin resistance represents the major driver of disease pathogenesis. Accordingly, any element constituting the metabolic syndrome, such as obesity, type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia, is linked to progression to NAFLD, and 85% of patients with NAFLD have at least one such condition [48]. In the general population, T2DM is also the strongest predictor for NASH-related hepatic fibrosis and cirrhosis [49, 50]. Studies in T2DM reported a prevalence of NAFLD and advanced liver fibrosis ranging from 65 to 73% and from 7.1 to 18%, respectively [51–53]. Based on these striking figures that far exceed those of the general population, several guidelines recommend screening for liver fibrosis in patients with T2DM [54, 55]. The classic metabolic components of the metabolic syndrome are more frequent in PWH. Diabetes is four times more prevalent in PWH compared with HIV-negative men [56]. A longitudinal study with a median follow-up of 4 years reported a cumulative incidence of T2DM of 10% in PWH, compared with 3% in uninfected controls [56]. Dyslipidemia is also a frequent finding in PWH, due to both chronic HIV infection and lifelong use of ART, particularly protease inhibitors (PIs) boosted with ritonavir [57]. Hypertension is also very common [58, 59]. Moreover, the increased prevalence of NASH in PWH was paralleled by the concomitant increase in overweight and obesity rate [60]. Besides insulin resistance, other factors contribute to the pathogenesis of NASH. Oxidative stress is thought to play an important role in perpetuating the chronic cellular damage in NASH pathogenesis. Accumulation of lipids in the hepatocyte impairs oxidative capacity of the mitochondria and stimulates peroxisomal and microsomal pathways of fat oxidation. As a consequence, increased generation of reactive oxygen species causes oxidative stress, triggers production of inflammatory cytokines (such as interleukin 6 and cytokeratin 18), and stimulates fibrogenesis and cell death [61••]. PWH have particularly high levels of markers of oxidative stress [62]. Genetic predisposition is undoubtedly participating risk factor in NASH pathogenesis. A genome-wide association scan of non-synonymous sequence variations (n = 9229) in a multiethnic population has identified an allele variant of the patatin-like phospholipase domain-containing 3 (*PNPLA3*) gene (rs738409; I148M) to be strongly linked to more hepatic inflammation and fat content deposition [63]. In the Multicenter AIDS Cohort Study, Price et al. found that *PNPLA3* (rs738409) non-CC genotype was associated with a higher prevalence of fatty liver (odds ratio, 3.30), but this was not confirmed by a subsequent study [64]. Adipose tissue dysfunction is another pathogenic factor that act through alteration of adipokines secretory profile from adipose tissue (↓adiponectin, ↑leptin), thus promoting development of NASH [65]. The gut microbiota has emerged as a potential player in the pathogenesis of NASH. Boursier et al. have documented an association between dysbiosis and histologic severity of NASH. In this study, an increased *Bacteroides*

Table 2 Incidence of NAFLD and/or significant/advanced liver fibrosis in HIV-infected patients

	Design/country	Sample	Age (years)	Duration HIV infection (years)	Diagnostic method
Rivero-Juarez [44]	Prospective/Spain 2013	210	44.3 ± 9.7	8.89 ± 5.3	TE > 7.2 kPa
Sebastiani [45]	Prospective/Canada 2015	796	43.5 (IQR 36–49.7)	6.3 (IQR 1.7–13.3)	Hepatic steatosis index > 36; FIB-4 > 3.25
Pembroke [46•]	Prospective/Canada 2017	313 (HIV and HIV/HCV)	50 (43–54)	15 (IQR 8–22)	CAP > 248 dB/m or transition to > 292 TE > 7.1 kPa or transition to > 12.5
Lallukka-Bruck [47]	Retrospective-prospective /Finland 2019	42	41.9 ± 1.3	23.5 ± 0.7	H-MRS, LFAT > 5.56% TE > 8.7 kPa/MRE > 3.62

	Duration follow-up	NAFLD	Liver fibrosis	Predictor of progression	
				Steatosis	Fibrosis
Rivero-Juarez [44]	18 months (IQR 12–26)	NA	10.9% (end of follow-up)	NA	No association with ART drugs and length of exposure to drugs
Sebastiani [45]	4.9 years (IQR 2.2–6.4)	6.9 per 100 PY (95% CI, 5.9–7.9)	0.9 per 100 PY (95% CI, 0.6–1.3)	Black ethnicity Lower level of albumin	Hyperglycemia Lower level of albumin
Pembroke [46•]	15.4 months (IQR 8.5–23.0)	37.8 per 100 PY (95% CI, 29.2–49.0)	12.7 per 100 PY (95% CI, 9.5–17.1)	NA	In HIV mono-infected: HIV duration, any grade of NAFL; in HIV/HCV: ↑ALT, HCV RNA
Lallukka-Bruck [47]	15.7 years (range 12.3–16.4)	Prevalence baseline versus end of follow-up: 35% versus 32%	9.5% (end of follow-up)	NA	NA

Continuous variables are expressed as mean ± standard deviation or median (interquartile range or range) and categorical variables are presented as percentages

ALT alanine aminotransferase; *ART* antiretroviral therapy; *CAP* controlled attenuation parameter; *CI* confidence interval; *HIV* human immunodeficiency virus; *HCV* hepatitis C virus; *H-MRS* proton magnetic resonance spectroscopy; *IQR* interquartile range; *LFAT* liver fat; *MRE* magnetic resonance elastography; *NA* not available; *NAFLD* nonalcoholic fatty liver disease; *PY* person-years; *TE* transient elastography

abundance was associated with NASH, while an increased *Ruminococcus* abundance with significant liver fibrosis [66]. HIV-induced alterations to the gut microbiota are common and associated with decreased diversity, with altered abundance of *Bacteroides*, *Ruminococcus*, and *Prevotella* [67]. Thus, it is conceivable that gut dysbiosis may also play a role in the increased frequency and severity of NASH observed in PWH. Finally, monocyte/macrophage activation (soluble CD163 and CD14) has also emerged as a new concept in the development of NAFLD and fibrosis, suggesting a Kupffer cell activation in the development of liver fibrosis [68]. Interestingly, soluble CD163 and CD14 have been associated with immune dysfunction, all-cause mortality, and liver fibrosis in PWH [69, 70].

HIV-Specific Risk Factors

Pathogenic factors that are unique to PWH may further contribute to the increased frequency and severity of NASH. Chronic HIV infection and associated inflammation could lead to immune-activating and pro-apoptotic effects of HIV on hepatocytes, including low-level HIV replication in hepatocytes possibly inducing liver fibrosis [71, 72]. Indeed, HIV viremia from ART interruptions is an independent risk factor for chronic elevated transaminases [73]. Although less frequent with more modern ART regimens, lipodystrophy is also a potential pathogenetic contributor to NASH in PWH. Lipodystrophy is a constellation of body composition and metabolic alterations characterized by a pathological accumulation of adipose tissue in the abdominal region, insulin resistance, and dyslipidemia [74, 75]. Lipodystrophy may occur in up to 80% of PWH treated with old ART regimens, particularly PIs, and persists after their discontinuation. NAFLD may frequently coexist with the features associated with this clinical entity [76]. Chronic elevation of ALT is noted in 20–30% of PWH on ART and is associated with histologic abnormalities, including NASH and fibrosis, in up to 60% of cases [33, 71, 77]. Old nucleoside reverse transcriptase inhibitors (NRTIs), particularly zidovudine, stavudine, and didanosine, can induce mitochondrial damage leading to impaired fatty acid oxidation responsible for microvesicular steatosis and lactic acidosis. These detrimental insults on the liver persist after discontinuation of those offending medications and are not fully reversible. Use of ritonavir-boosted PIs (darunavir, indinavir, lopinavir) is commonly associated with elevation in transaminases and direct hepatocyte stress [78]. Importantly, boosted PIs cause more lipodystrophy, dyslipidemia, and insulin resistance, than other ART regimens, thus contributing to NASH through their link with metabolic complications [79]. Despite integrase inhibitors being associated with a safer metabolic profile and less frequent dyslipidemia [80], recent data suggest increased weight gain, especially in black African women [81]. Studies on prevalence of NAFLD and

NASH also investigated associated cofactors in PWH, thus providing further information on main pathogenic factors. The most consistently reported cofactor associated with NAFLD is body mass index (BMI), followed by triglycerides and T2DM [37, 38, 40, 41, 46]. On the other hand, lean NAFLD, defined as NAFLD in patients with BMI < 25 Kg/m^2, seems a frequent clinical entity in PWH, affecting 24.2% of lean patients and representing 35.4% of all NAFLD patients [82]. Although high suspicion of NAFLD is recommended in overweight PWH, NAFLD should be considered also in older lean patients with dyslipidemia or elevated ALT. Some HIV-related cofactors have also been associated with NAFLD, including low CD4 cell count and exposure to NRTIs [38, 41]. Overall, the pathogenesis of NASH in the setting of HIV infection is much more complex than HIV-negative NASH and still only partly understood, due to both HIV itself and the long-lasting exposure to ART, together with frequent metabolic comorbidities.

Natural History

The key histopathological event in the natural history of a chronic liver disease of any etiology is the formation of liver fibrosis. The accumulation of fibrosis eventually leads to progressive distortion of the hepatic architecture that is the hallmark of evolution to cirrhosis. In patients with NAFLD, the estimation of liver fibrosis is essential for risk stratification and prediction of liver-related complications and all-cause mortality [83]. Liver fibrosis can also be seen as a proxy for NASH given that simple steatosis without necrotic-inflammatory changes (NAFL) has a much slower fibrosis progression. Indeed, liver fibrosis progresses of 1 stage every 7 years for patients with NASH, compared with 1 stage every 14 years for simple NAFL [84]. However, ~20% of patients with NAFL (no fibrosis) may progress to advanced fibrosis within a relatively short period. Presence of stage 2 or higher liver fibrosis is an independent predictor of mortality [83]. The prevalence of significant liver fibrosis due to NAFLD in HIV mono-infected ranges widely from 3.6 to 35.7% [85, 86] (Tables 1 and 2). The meta-analysis by Maurice et al. collocates this figure at 22%, higher than that reported in the HIV-negative NAFLD population [24••]. Overall, there are very few studies investigating the natural history of NASH in the setting of HIV infection, and all of them are based on non-invasive diagnostic modalities rather than liver histology (Table 2). The incidence rate of NAFLD reported in the general population varies across the world, ranging from 2.8 to 5.2 per 100 person-years (PY) [20]. In HIV mono-infected patients, incidence of NAFLD by a simple steatosis biomarker has been reported at 6.9 per 100 PY (95% CI, 5.9–7.9) [45], while another study employing magnetic resonance spectroscopy reported no incident NAFLD during a follow-up period of 15.7 years [47]. In the LIVEr disease in HIV (LIVEHIV) cohort study from our team, the incidence of significant liver fibrosis in HIV mono-infected patients was reported at 0.9 per 100 PY by employing the serum biomarker FIB-4. In the same cohort, progression of liver fibrosis by transient elastography (TE), defined as developing significant liver fibrosis or liver cirrhosis, was determined at 12.7 per 100 PY, which is higher than the general population [45, 46]. Similar figures were reported by Rivero-Juarez and colleagues [44]. Even less data are available for clinical outcomes related to NAFLD in HIV mono-infected patients. In the general HIV-uninfected population, the 10-year mortality reported in 3869 NAFLD subjects was 10.2%, which is higher than controls (7.6%) [87]. NAFLD was also an independent risk factor for incident metabolic comorbidities and death. A study of 1092 patients from the LIVEHIV cohort reported an incidence rate of liver-related events (decompensation, HCC, death) of 8.6 per 1000 PY, without significant difference between HIV mono-infected and HIV/HCV co-infected patients [88]. This rate seems higher than that reported in HIV-negative NAFLD [89]. Beyond the liver, there is a growing body of evidence indicating that NAFLD is a multisystem disease affecting extra-hepatic organs, possibly due to a chronic inflammatory *milieu* and impacting on health-related quality of life [90–92]. NAFLD is a risk factor for all-cause mortality due to cardiovascular disease and cancer, which represent the two leading causes of death in this population [83, 93]. NAFLD patients also exhibit a higher risk of developing incident T2DM, chronic kidney disease, cognitive impairment, and vasculopathy [94–97]. Given that HIV infection is also a multi-system disease, NAFLD could lead to a potential higher risk for extra-hepatic manifestations. HIV itself carries higher risk of both cardiovascular and kidney disease, and of cognitive impairment [98–100]. Only one study has investigated the effect of NAFLD on the incidence of important metabolic comorbidities in PWH, including T2DM, hypertension, dyslipidemia, and kidney disease. Krahn et al. followed 485 patients from the LIVEHIV cohort for a median of 40.1 months, reporting an increased incidence of T2DM and dyslipidemia in HIV mono-infected patients with NAFLD compared with those without NAFLD [101]. This finding has relevant risk stratification implications, given that PWH have already an increased cardiovascular risk compared with HIV-negative persons, and these metabolic comorbidities may further contribute to cardiovascular morbidity and mortality.

Overall, an inter-play between two multi-system diseases, chronic HIV and NAFLD, could be responsible for these findings. The European AIDS Clinical Society guidelines already recommend screening for NAFLD in PWH with metabolic syndrome, and expansion of these criteria to patients with any metabolic comorbidity has been proposed [102, 103]. Considering the significant incidence of NAFLD and associated liver fibrosis in PWH, there are too few longitudinal data

investigating outcomes of NAFLD so far. Future research efforts should also target effect of NAFLD on cardiovascular outcomes and all-cause mortality in the specific setting of HIV infection.

Diagnosis

On June 12, 2018, the first international NASH day was named "NASH: a silent killer." Indeed, a diagnosis of NASH and associated liver fibrosis based on physical examination and routine blood exams is difficult as most patients only show evident clinical signs when their disease is already advanced, at the cirrhotic stage. Up to 79% of patients with NAFLD, 46% of those with NASH, and 20% of patients with advanced liver fibrosis may have normal ALT [104, 105]. Therefore, early diagnosis of NASH is pivotal to establish prognosis, management, and treatment. Early interventions such as alcohol abstinence and control of the metabolic risk factors may reduce the progression towards end-stage liver disease. Also, patients with liver cirrhosis require specific surveillance, including screening for esophageal varices and HCC [106]. Finally, while liver transplant is the only curative treatment for end-stage liver disease, the limited availability of donor organs is problematic. Liver biopsy is considered the gold standard of reference to diagnose NASH and associated liver fibrosis [54]. Indeed, despite many research efforts to identify an accurate serum biomarker to diagnose NASH, a diagnosis of NASH is still based on histologic coexistence of hepatic steatosis, necroinflammatory changes, and hepatocyte ballooning. However, liver biopsy is invasive, costly, and prone to sampling error [107, 108]. Complexity barriers to biopsy may have limited the numbers of studies investigating NASH in PWH. Moreover, studies that have relied on biopsy may suffer from selection biases, such as inclusion of patients with elevated ALT only. Although histology is still necessary for a definitive diagnosis of NASH, the co-existence of NAFLD and liver fibrosis also likely indicates the presence of NASH. Several non-invasive tools for the diagnosis of NAFLD and associated liver fibrosis have been extensively studied in the setting of HIV-negative NAFLD. These methods rely on two different approaches: a biological approach, based on the quantification of biomarkers in the serum, and a physical approach, based on the measurement of liver stiffness by either ultrasonographic elastography techniques or magnetic resonance elastography [109]. Few of these methods have been validated in the specific setting of HIV infection (Table 3). These include TE with associated controlled attenuation parameter (CAP), a software that quantifies liver fat content concomitantly with liver stiffness measurement, and serum fibrosis and steatosis biomarkers [16, 43, 110, 113–115]. Two studies validated these methods against the gold standard, liver histology. In 66 HIV mono-infected patients, Morse and colleagues evaluated the performance of TE against three serum fibrosis biomarkers, AST-to-Platelets Ratio Index (APRI), FIB-4, and NAFLD fibrosis score. The authors found that TE outperformed the simple serum biomarkers, with an area under the curve (AUC) of 0.93 and a sensitivity and specificity of 93% and 73%, respectively, to detect significant liver fibrosis with a cut-off value of 7.1 kPa [112]. Another recent study by Lemoine et al. reported on the performance of several non-invasive diagnostic tests for hepatic steatosis, NASH, and fibrosis in 49 HIV mono-infected patients with available histology [116••]. Overall, the researchers reported high AUC for magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) and CAP, with an AUC of 0.98 and 0.87, respectively. Interestingly, an ALT cut-off value of 36 had an AUC of 0.88 for the diagnosis of NASH, with 91% and 77% sensitivity and specificity, respectively. In this study, serum fibrosis biomarkers such as APRI and FIB-4 had higher performance than TE for the diagnosis of significant liver fibrosis. A poor concordance between serum fibrosis biomarkers and TE in the specific setting of HIV infection has been reported [117]. In a study of 17 patients with NASH diagnosed by both liver histology and the biomarker of cytokeratin 18, Benmassaoud et al. found that TE had a high AUC at 0.91 to diagnose significant liver fibrosis in patients with a non-invasive diagnosis of NASH [42]. Another important diagnostic aspect of clinical practice related to NASH is the diagnosis of esophageal varices requiring primary prophylaxis in patients with liver cirrhosis [11, 12]. Esophageal varices requiring primary prophylaxis are not frequent in patients with compensated cirrhosis, and access to esophagogastroduodenoscopy can be problematic in the context of primary and secondary care HIV clinics. The Baveno VI guidelines were proposed to reduce the number of unnecessary endoscopies in patients with liver cirrhosis if the TE value was < 20 kPa and platelet count $> 150{,}000/\mu L$ [118]. In a recent multicenter study, we have validated these criteria in 507 PWH with TE > 10 kPa, including 42 HIV mono-infected patients with suspected NAFLD, demonstrating that the Baveno VI criteria can safely spare at least 33.3% screening endoscopy [119]. These findings can be used for resource optimization to select HIV-infected patients who need to undergo an esophagogastroduodenoscopy. In Fig. 1, we propose an algorithm for the diagnosis, management, and follow-up for suspected NAFLD and associated liver fibrosis in HIV-infected patients with comorbidities. We combined already existing European AIDS Clinical Society (EACS) and European Association for the Study of the Liver (EASL) guidelines with findings of more recent studies.

Table 3 Diagnostic non-invasive tool of NAFLD, NASH, and fibrosis in HIV mono-infected patients

	Diagnostic test	Cut-off	AUROCs (95% CI)	Se (%)	Sp (%)	PPV (%)	NPV (%)
NAFLD [45, 110, 111]	CAP (dB/m)	> 280	87 (76–99)	86	72	72	86
		> 238	88 (78–99)	89	80	NA	NA
	MRI-PDFF (%)	> 10	98 (96–100)	91	81	81	91
	HSI	> 36	88 (80–95)	85.7	84.1	63.2	94.9
NASH [111]	NashTest	> 0.75	64 (48–80)	17	85	50	54
	ALT (IU/L)	> 36	88 (77–99)	91	77	78	91
Significant liver fibrosis (≥ F2) [42, 111, 112]	TE (kPa)	≥ 7.1	61 (43–79)	80	32	39	75
		≥ 7.1	93 (86–99)	93	73	52	97
		≥ 7.1 (in patients with NAFLD and elevated CK-18)	91 (81–100)	NA	NA	NA	NA
	FIB-4	< 1.45	81 (67–95)	87	50	43	89
		> 2.67	64 (49–79)	21	89	38	78
	APRI	< 0.5	86 (74–98)	87	68	54	92
		> 1.5	61 (46–77)	21	82	27	77
	NFS	> 0.676	70 (55–85)	14	96	50	78
		< − 1.46	71 (57–86)	87	56	46	90

All the diagnostic tests were compared with liver biopsy, except [110] which was compared with MRS liver fat fraction ≥ 0.05 and [45] which was compared with ultrasound

APRI AST-to-Platelets Ratio Index; *CAP* controlled attenuation parameter; *CI* confidence interval; *CK-18* cytokeratin 18; *FIB-4* fibrosis-4 score; *HSI* hepatic steatosis index; *MRI-PDFF* magnetic resonance imaging proton density fat fraction; *NAFLD* nonalcoholic fatty liver disease; *NASH* nonalcoholic steatohepatitis; *NFS* NAFLD fibrosis score; *NPV* negative predictive value; *PPV* positive predictive value; *Se* sensitivity; *Sp* specificity; *TE* transient elastography; *IU* international unit

Treatment

Treatment for NASH is aimed to improve outcomes, such as reduce NASH-related mortality and progression to cirrhosis and HCC.

Lifestyle Changes

The first-line treatment for NASH is weight loss, through a combination of lifestyle changes including calorie reductions, exercise, and healthy eating [111]. Since the most frequent reported predictor of NAFLD in PWH is BMI, it is reasonable that these interventions may also be effective in HIV-associated NAFLD, although ad hoc studies are lacking. In the general NAFLD population, suggested interventions for weight loss include 500–1000 kcal energy defect to induce a weight loss of 500–1000 g/week, targeting a total of 7–10% weight loss [54]. Weight loss of > 7% can lead to resolution of NASH, while a weight loss > 10% can regress liver fibrosis [120]. Weight loss targets to achieve fibrosis improvement have not been determined, and rapid weight loss is not recommended for patients with advanced liver disease due to risk of malnutrition and deconditioning. Other important components of an appropriate lifestyle modification in the context of NASH include reducing alcohol intake, avoiding fructose-containing beverages and food, and limiting the consumption of processed red meat [54, 121]. Interestingly, a recent randomized controlled trial conducted in HIV-negative patients with NAFLD showed significant reduction of liver fat, ALT, Framingham risk score, cholesterol, and insulin resistance after 12 weeks of ad libitum Mediterranean diet [122]. In this study, the Mediterranean diet was based on foods consumed in traditional Cretan diet, with target macronutrient energy distributed as follows: 40% from carbohydrate, 35–40% from fat (with < 10% of energy as saturated fat), and 20% of energy as protein. This approach was both efficacious and able to provide long-term adherence to intervention diets but has yet to be tested in PWH.

ART-Related Interventions

An intervention specific to the HIV setting may be related to the use of ART with a lower potential to induce hepatic steatosis or metabolic disturbances. In a retrospective cohort study, maraviroc, a chemokine receptor 5 antagonist, showed a potential protective role in reducing the incidence of NAFLD in PWH [123]. In a randomized controlled trial, Macias and colleagues study the effect of switching efavirenz to raltegravir on hepatic steatosis diagnosed by TE with CAP among 39 HIV/HCV co-infected patients. At week 48, resolution of hepatic steatosis was observed in 47% patients switched to raltegravir compared with only 15% of patients who were maintained on efavirenz [124]. However, recent data suggest that regimens containing integrase inhibitors,

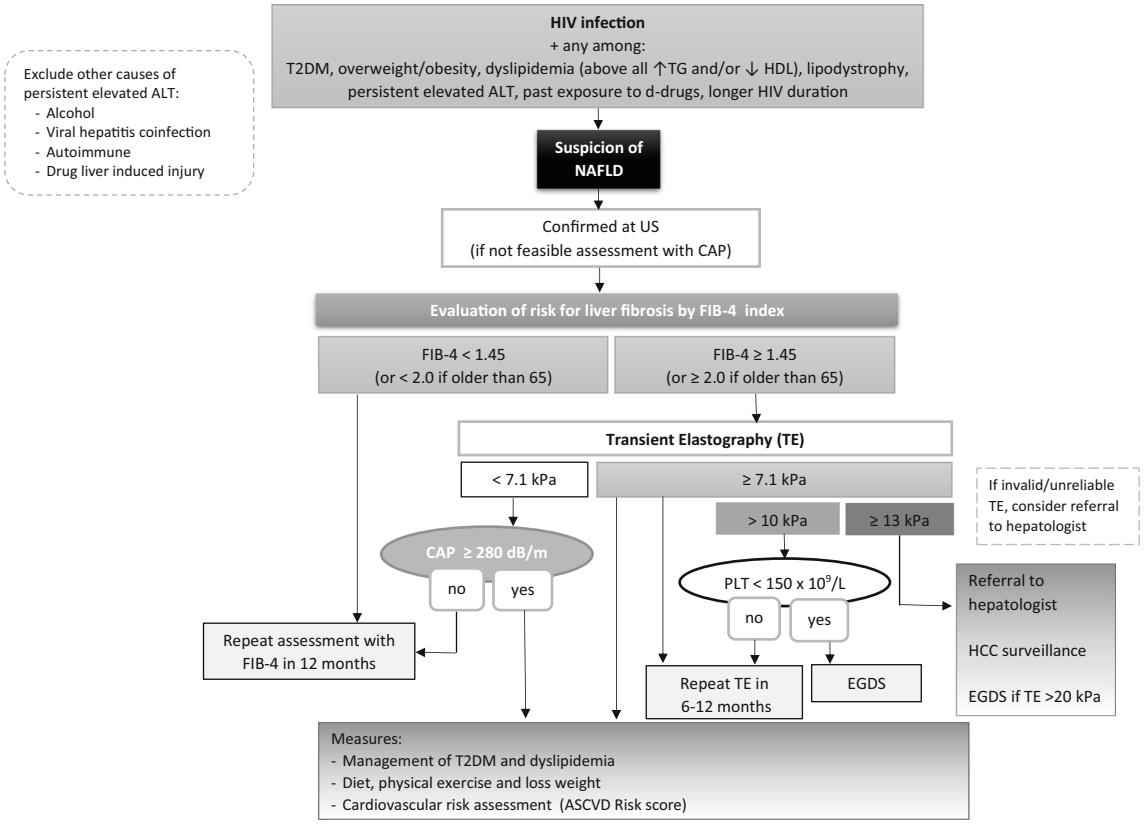

Fig. 1 Flow chart for diagnosis, management and follow-up of NAFLD and associated liver fibrosis in HIV infected patients. Abbreviations: ALT, alanine aminotransferase; ASCVD, atherosclerotic cardiovascular disease; CAP, controlled attenuation parameter; EGDS, esophagogastroduodenoscopy; HCC, hepatocellular carcinoma; HDL, high density lipoprotein; HIV, human immunodeficiency virus; FIB-4, fibrosis 4 index; NAFLD, nonalcoholic fatty liver disease; PLT, platelets; T2DM, type 2 diabetes mellitus; TE, transient elastography; TG, triglycerides; US, ultrasound

and in particular dolutegravir, may be associated with weight gain [81]. Further studies with larger sample sizes and longer follow-up are warranted.

Pharmacologic Therapy

In terms of pharmacologic interventions, there are multiple ongoing clinical trials investigating different compounds targeting various metabolic, inflammatory, and fibrogenic pathways in NASH. However, few approaches have been tested in the specific context of HIV infection as PWH are currently excluded from global NASH clinical trials. In a recent statement from the Steatohepatitis in HIV Emerging Research network, inclusion of PWH in these global trials has been advocated on the basis of the high prevalence and severity of the disease in this population [125••]. In the context of HIV-associated lipodystrophy, the use of pioglitazone, a thiazolidinedione insulin-sensitizing agent used for treatment of HIV-negative NASH, has been shown to reduce liver fat and lobular inflammation in 13 PWH, but did not achieve the primary endpoint of improvement or resolution of NASH [126]. The ARRIVE trial, a double-blind, randomized, placebo-controlled trial, tested the efficacy of 12 weeks of treatment with aramchol, a fatty acid-bile acid conjugated stearoyl coenzyme A desaturase 1, versus placebo in 25 PWH with NAFLD. Over a 12-week period, there was no significant change of hepatic fat or body fat as assessed by using the MRI-PDFF [127]. In a phase 4 open-label clinical trial, one of us used vitamin E 800 IU daily for 24 weeks in 27 HIV mono-infected patients with NASH [128•]. Vitamin E is an antioxidant used as first-line pharmacologic treatment for NASH in HIV-negative patients [54]. In this study, we found a significant decrease in ALT (− 27 units/L), steatosis estimated by CAP (− 22 dB/m), and cytokeratin-18 (− 123 units/L). However, there was no improvement in liver fibrosis, possibly due to the short duration of the trial. Another molecule recently tested in PWH with NAFLD is tesamorelin, a synthetic form of growth hormone–releasing hormone, approved for the treatment of excess abdominal fat in HIV-associated lipodystrophy. Stanley et al. assessed the effect of tesamorelin on steatosis and histology in a randomized multicenter trial including 61 PWH with NAFLD [129]. After 12 months of treatment, steatosis in patients on treatment arm had decreased by 32% from baseline, while it had increased by 5% in

placebo patients. Moreover, 35% of patients in the tesamorelin group resolved steatosis in comparison with only 4% of patients on placebo. The study also found that 10.5% of patients in the tesamorelin group experienced progression of liver fibrosis compared with 37.5% in patients receiving a placebo.

Bariatric Surgery

Bariatric surgery provides an option for durable weight loss in obese NAFLD patients, with significant improvement in both associated metabolic syndrome comorbidities and liver fibrosis. Weight-loss surgery is being increasingly considered in morbidly obese PWH [130]. However, consideration should be provided to variable ART absorption after weight-loss surgery [131].

Conclusion

NAFLD is a clinical entity that frequently coexists in the setting of HIV infection. Progression of NAFL to NASH should be highly suspected in case of elevated ALT, overweight and if serum fibrosis biomarkers or TE indicate significant liver fibrosis. Screening for NAFLD should be implemented at least in patients with metabolic syndrome and considered in PWH with any metabolic comorbidities or elevated ALT. Indeed, any patients with NAFLD should undergo risk stratification based on liver fibrosis staging, surveillance for HCC, and gastroesophageal varices in case of liver cirrhosis and appropriate therapeutic interventions. Future research efforts should include longitudinal studies characterizing the natural history of NASH, identification of biomarkers to diagnose NASH, and fibrosis progression in the specific setting of HIV, along with targeted interventions that will improve clinical outcomes in PWH.

Authors' Contributions AC contributed to the conception, study design, data, and interpretation of the data. GS contributed to the conception, study design, data, and interpretation of the data and first draft of the manuscript. MS and KP contributed to the interpretation of data. All authors approved the final version of the article.

Funding GS is supported by a Junior 1 and 2 Salary Award from FRQS (#27127 and #267806) and research salary from the Department of Medicine of McGill University.

Compliance with Ethical Standards

Conflict of Interest KP is an advisory board/consultant for Gilead Sciences, Intercept, Novartis, and Eli Lilly, and received research funding from Gilead Sciences. GS has acted as speaker for Merck, Gilead, Abbvie, Novonordisk, and Novartis, served as an advisory board member for Merck, Novartis, Gilead, and Intercept, and has received unrestricted research funding from Merck and Theratec. AC and MS have nothing to disclose.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Organization WH. https://www.who.int/gho/hiv/en/. Accessed 9 May 2020.
2. CDC. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas—2015. HIV Surveillance Supplemental Report. 2017;22(2).
3. Lloyd-Smith E, Brodkin E, Wood E, Kerr T, Tyndall MW, Montaner JS, et al. Impact of HAART and injection drug use on life expectancy of two HIV-positive cohorts in British Columbia. AIDS. 2006;20(3):445–50.
4. Fang CT, Chang YY, Hsu HM, Twu SJ, Chen KT, Lin CC, et al. Life expectancy of patients with newly-diagnosed HIV infection in the era of highly active antiretroviral therapy. Qjm. 2007;100(2):97–105.
5. Lewden C, May T, Rosenthal E, Burty C, Bonnet F, Costagliola D, et al. Changes in causes of death among adults infected by HIV between 2000 and 2005: the "Mortalite 2000 and 2005" surveys (ANRS EN19 and Mortavic). J Acquir Immune Defic Syndr. 2008;48(5):590–8.
6. Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. Lancet. 2014;384(9939):241–8.
7. Palmer AK, Klein MB, Raboud J, Cooper C, Hosein S, Loutfy M, et al. Cohort profile: the Canadian Observational Cohort collaboration. Int J Epidemiol. 2011;40(1):25–32.
8. Rosenthal E, Salmon-Ceron D, Lewden C, Bouteloup V, Pialoux G, Bonnet F, et al. Liver-related deaths in HIV-infected patients between 1995 and 2005 in the French GERMIVIC Joint Study Group Network (Mortavic 2005 study in collaboration with the Mortalite 2005 survey, ANRS EN19). HIV Med. 2009;10(5):282–9.
9. Sahasrabuddhe VV, Shiels MS, McGlynn KA, Engels EA. The risk of hepatocellular carcinoma among individuals with acquired immunodeficiency syndrome in the United States. Cancer. 2012.
10.• Kaspar MB, Sterling RK. Mechanisms of liver disease in patients infected with HIV. BMJ Open Gastroenterol. 2017;4(1):e000166 **This is a comprehensive review focusing on pathogenic mechanisms of liver disease in the specific setting of HIV infection, including NAFLD.**
11. Organization WH. Global action plan for the prevention and control of noncommunicable diseases 2013–2020. Geneva: World Health Organization; 2013. https://www.who.int/bulletin/volumes/97/2/18-213777/en/. Accessed 9 May 2020.
12. 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(1):124–31.
13. 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. 2002;35(2):367–72.
14. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. Diabetes. 2001;50(8):1844–50.

15. Ratziu V, Bellentani S, Cortez-Pinto H, Day C, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. J Hepatol. 2010;53(2):372–84.
16. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology. 2012;55(6):2005–23.
17. Udompap P, Kim D, Kim WR. Current and future burden of chronic nonmalignant liver disease. Clin Gastroenterol Hepatol. 2015;13(12):2031–41.
18. Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. Gastroenterology. 2011;141(4):1249–53.
19. Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology. 2015;148(3):547–55.
20. Younossi ZM. The epidemiology of nonalcoholic steatohepatitis. Clin Liver Dis (Hoboken). 2018;11(4):92–4.
21. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005;41(6):1313–21.
22. Taylor RS, Taylor RJ, Bayliss S, Hagstrom H, Nasr P, Schattenberg JM, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. Gastroenterology. 2020;158(6):1611–25 e12.
23. Bedossa P, Consortium FP. Utility and appropriateness of the fatty liver inhibition of progression (FLIP) algorithm and steatosis, activity, and fibrosis (SAF) score in the evaluation of biopsies of nonalcoholic fatty liver disease. Hepatology. 2014;60(2):565–75.
24.•• 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. 2017;31(11):1621–32 **This meta-analysis of 10 studies reports on prevalence and predictors of NAFLD, NASH, and liver fibrosis in HIV mono-infected patients.**
25. 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 Diseases : an official publication of the Infectious Diseases Society of America. 2008;47(2):250–7.
26. Nishijima T, Gatanaga H, Shimbo T, Komatsu H, Nozaki Y, Nagata N, et al. Traditional but not HIV-related factors are associated with nonalcoholic fatty liver disease in Asian patients with HIV-1 infection. PLoS One. 2014;9(1):e87596.
27. Macias J, Gonzalez J, Tural C, Ortega-Gonzalez E, Pulido F, Rubio R, et al. Prevalence and factors associated with liver steatosis as measured by transient elastography with controlled attenuation parameter in HIV-infected patients. AIDS. 2014;28(9):1279–87.
28. Lui G, Wong VW, Wong GL, Chu WC, Wong CK, Yung IM, et al. Liver fibrosis and fatty liver in Asian HIV-infected patients. Aliment Pharmacol Ther. 2016;44(4):411–21.
29. Lombardi R, Lever R, Smith C, Marshall N, Rodger A, Bhagani S, et al. Liver test abnormalities in patients with HIV mono-infection: assessment with simple noninvasive fibrosis markers. Ann Gastroenterol. 2017;30(3):349–56.
30. Price JC, Ma Y, Scherzer R, Korn N, Tillinghast K, Peters MG, et al. Human immunodeficiency virus-infected and uninfected adults with non-genotype 3 hepatitis C virus have less hepatic steatosis than adults with neither infection. Hepatology. 2017;65(3):853–63.
31. Lemoine M, Barbu V, Girard PM, Kim M, Bastard JP, Wendum D, et al. Altered hepatic expression of SREBP-1 and PPARgamma is associated with liver injury in insulin-resistant lipodystrophic HIV-infected patients. AIDS. 2006;20(3):387–95.
32. Crum-Cianflone N, Collins G, Medina S, Asher D, Campin R, Bavaro M, et al. Prevalence and factors associated with liver test abnormalities among human immunodeficiency virus-infected persons. Clin Gastroenterol Hepatol. 2010;8(2):183–91.
33. Ingiliz P, Valantin MA, Duvivier C, Medja F, Dominguez S, Charlotte F, et al. Liver damage underlying unexplained transaminase elevation in human immunodeficiency virus-1 mono-infected patients on antiretroviral therapy. Hepatology. 2009;49(2):436–42.
34. Sterling RK, Smith PG, Brunt EM. Hepatic steatosis in human immunodeficiency virus: a prospective study in patients without viral hepatitis, diabetes, or alcohol abuse. J Clin Gastroenterol. 2013;47(2):182–7.
35. 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(10):1569–78.
36.• Vodkin I, Valasek MA, Bettencourt R, Cachay E, Loomba R. Clinical, biochemical and histological differences between HIV-associated NAFLD and primary NAFLD: a case-control study. Aliment Pharmacol Ther. 2015;41(4):368–78 **This is the only case–control study comparing features of HIV-associated NAFLD and HIV-negative NAFLD. It showed that HIV-associated NAFLD has increased severity of liver disease and higher prevalence of NASH.**
37. Vuille-Lessard E, Lebouche B, Lennox L, Routy JP, Costiniuk CT, Pexos C, et al. Nonalcoholic fatty liver disease diagnosed by transient elastography with controlled attenuation parameter in unselected HIV monoinfected patients. AIDS. 2016;30(17):2635–43.
38. 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 mono-infection. Dig Liver Dis. 2016;48(12):1471–7.
39. Prat LI, Roccarina D, Lever R, Lombardi R, Rodger A, Hall A, et al. Aetiology and severity of liver disease in HIV positive patients with suspected NAFLD: lessons from a cohort with available liver biopsies. J Acquir Immune Defic Syndr 2018.
40. Mohr R, Boesecke C, Dold L, Schierwagen R, Schwarze-Zander C, Wasmuth JC, et al. Return-to-health effect of modern combined antiretroviral therapy potentially predisposes HIV patients to hepatic steatosis. Medicine. 2018;97(17):e0462.
41. Perazzo H, Cardoso SW, Yanavich C, Nunes EP, Morata M, Gorni N, et al. Predictive factors associated with liver fibrosis and steatosis by transient elastography in patients with HIV mono-infection under long-term combined antiretroviral therapy. J Int AIDS Soc. 2018;21(11):e25201.
42. Benmassaoud A, Ghali P, Cox J, Wong P, Szabo J, Deschenes M, et al. Screening for nonalcoholic steatohepatitis by using cytokeratin 18 and transient elastography in HIV mono-infection. PLoS One. 2018;13(1):e0191985.
43. Feldstein AE, Wieckowska A, Lopez AR, Liu YC, Zein NN, McCullough AJ. Cytokeratin-18 fragment levels as noninvasive biomarkers for nonalcoholic steatohepatitis: a multicenter validation study. Hepatology. 2009;50(4):1072–8.
44. Rivero-Juarez A, Camacho A, Merchante N, Perez-Camacho I, Macias J, Ortiz-Garcia C, et al. Incidence of liver damage of uncertain origin in HIV patients not co-infected with HCV/HBV. PLoS One. 2013;8(7):e68953.

45. Sebastiani G, Rollet-Kurhajec KC, Pexos C, Gilmore N, Klein MB. Incidence and predictors of hepatic steatosis and fibrosis by serum biomarkers in a large cohort of human immunodeficiency virus mono-infected patients. Open forum Infect Diseases. 2015;2(1):ofv015.
46.• Pembroke T, Deschenes M, Lebouche B, Benmassaoud A, Sewitch M, Ghali P, et al. Hepatic steatosis progresses faster in HIV mono-infected than HIV/HCV co-infected patients and is associated with liver fibrosis. J Hepatol. 2017;67(4):801–8 **One of the very few studies investigating the natural history of fatty liver in HIV-infected patients. In particular, they found that HIV mono-infected patients have faster fatty liver progression than HIV/HCV co-infected patients.**
47. Lallukka-Bruck S, Isokuortti E, Luukkonen PK, Hakkarainen A, Lundbom N, Sutinen J, et al. Natural course of nonalcoholic fatty liver disease and type 2 diabetes in patients with human immunodeficiency virus with and without combination antiretroviral therapy-associated lipodystrophy: a 16-year follow-up study. Clin Infect Dis. 2020;70(8):1708–16.
48. Gariani K, Philippe J, Jornayvaz FR. Non-alcoholic fatty liver disease and insulin resistance: from bench to bedside. Diabetes Metab. 2013;39(1):16–26.
49. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc. 1980;55(7):434–8.
50. Diehl AM, Goodman Z, Ishak KG. Alcohollike liver disease in nonalcoholics. A clinical and histologic comparison with alcohol-induced liver injury. Gastroenterology. 1988;95(4):1056–62.
51. de Ledinghen V, Vergniol J, Gonzalez C, Foucher J, Maury E, Chemineau L, et al. Screening for liver fibrosis by using FibroScan((R)) and FibroTest in patients with diabetes. Dig Liver Dis. 2012;44(5):413–8.
52. Kwok R, Choi KC, Wong GL, Zhang Y, Chan HL, Luk AO, et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. Gut. 2016;65(8):1359–68.
53. Doycheva I, Cui J, Nguyen P, Costa EA, Hooker J, Hofflich H, et al. Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE. Aliment Pharmacol Ther. 2016;43(1):83–95.
54. European Association for the Study of the L, European Association for the Study of D, European Association for the Study of O. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402.
55. Introduction. Standards of medical care in diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S1-S2.
56. Brown TT, Cole SR, Li X, Kingsley LA, Palella FJ, Riddler SA, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. Arch Intern Med. 2005;165(10):1179–84.
57. 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–S56.
58. Feeney ER, Mallon PW. HIV and HAART-associated dyslipidemia. Open Cardiovasc Med J. 2011;5:49–63.
59. Hadigan C, Meigs JB, Corcoran C, Rietschel P, Piecuch S, Basgoz N, et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. Clin Infect Dis. 2001;32(1):130–9.
60. Crum-Cianflone N, Roediger MP, Eberly L, Headd M, Marconi V, Ganesan A, et al. Increasing rates of obesity among HIV-infected persons during the HIV epidemic. PLoS One. 2010;5(4):e10106.
61.•• Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328–57 **These are clinically useful guidelines about all major aspects of NAFLD including disease definitions and treatment recommendations.**
62. Ivanov AV, Valuev-Elliston VT, Ivanova ON, Kochetkov SN, Starodubova ES, Bartosch B, et al. Oxidative stress during HIV infection: mechanisms and consequences. Oxidative Med Cell Longev. 2016;2016:8910396.
63. Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet. 2008;40(12):1461–5.
64. Dold L, Luda C, Schwarze-Zander C, Boesecke C, Hansel C, Nischalke HD, et al. Genetic polymorphisms associated with fatty liver disease and fibrosis in HIV positive patients receiving combined antiretroviral therapy (cART). PLoS One. 2017;12(6):e0178685.
65. Polyzos SA, Kountouras J, Mantzoros CS. Adipokines in nonalcoholic fatty liver disease. Metab Clin Exp. 2016;65(8):1062–79.
66. Boursier J, Diehl AM. Nonalcoholic fatty liver disease and the gut microbiome. Clin Liver Dis. 2016;20(2):263–75.
67. Zevin AS, McKinnon L, Burgener A, Klatt NR. Microbial translocation and microbiome dysbiosis in HIV-associated immune activation. Curr Opin HIV AIDS. 2016;11(2):182–90.
68. Kazankov K, Barrera F, Moller HJ, Rosso C, Bugianesi E, David E, et al. The macrophage activation marker sCD163 is associated with morphological disease stages in patients with non-alcoholic fatty liver disease. Liver Int. 2016;36(10):1549–57.
69. Lemoine M, Lacombe K, Bastard JP, Sebire M, Fonquernie L, Valin N, et al. Metabolic syndrome and obesity are the cornerstones of liver fibrosis in HIV-monoinfected patients: results of the METAFIB study. AIDS. 2017;31:1955–64.
70. Kirkegaard-Klitbo DM, Mejer N, Knudsen TB, Moller HJ, Moestrup SK, Poulsen SD, et al. Soluble CD163 predicts incident chronic lung, kidney and liver disease in HIV infection. AIDS. 2017;31(7):981–8.
71. Kovari H, Weber R. Influence of antiretroviral therapy on liver disease. Curr Opin HIV AIDS. 2011;6(4):272–7.
72. Kong L, Cardona Maya W, Moreno-Fernandez ME, Ma G, Shata MT, Sherman KE, et al. Low-level HIV infection of hepatocytes. Virol J. 2012;9:157.
73. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med. 2006;355(22):2283–96.
74. Singhania R, Kotler DP. Lipodystrophy in HIV patients: its challenges and management approaches. HIV AIDS (Auckl). 2011;3:135–43.
75. Falutz J. Management of fat accumulation in patients with HIV infection. Curr HIV/AIDS Rep. 2011;8(3):200–8.
76. Ryan P, Blanco F, Garcia-Gasco P, Garcia-Merchan J, Vispo E, Barreiro P, et al. Predictors of severe hepatic steatosis using abdominal ultrasound in HIV-infected patients. HIV Med. 2009;10(1):53–9.
77. Nunez M. Clinical syndromes and consequences of antiretroviral-related hepatotoxicity. Hepatology. 2010;52(3):1143–55.
78. Sulkowski MS, Mehta SH, Chaisson RE, Thomas DL, Moore RD. Hepatotoxicity associated with protease inhibitor-based antiretroviral regimens with or without concurrent ritonavir. AIDS. 2004;18(17):2277–84.
79. Sulkowski MS, Mehta SH, Torbenson M, Afdhal NH, Mirel L, Moore RD, et al. Hepatic steatosis and antiretroviral drug use among adults coinfected with HIV and hepatitis C virus. AIDS. 2005;19(6):585–92.
80. Eron JJ, Young B, Cooper DA, Youle M, Dejesus E, Andrade-Villanueva J, et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-

infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. Lancet. 2010;375(9712):396–407.
81. Bourgi K, Rebeiro PF, Turner M, Castilho JL, Hulgan T, Raffanti SP, et al. Greater weight gain in treatment naive persons starting dolutegravir-based antiretroviral therapy. Clin Infect Dis. 2019.
82. Cervo A, Milic J, Mazzola G, Schepis F, Petta S, Krahn T, Lebouche B, Deschenes M, Cascio A, Guaraldi G, Sebastiani G Prevalence, predictors and severity of lean non-alcoholic fatty liver disease in HIV-infected patients. Clin Infect Dis 2020.
83. Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. Hepatology. 2017;65(5):1557–65.
84. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol. 2015;13(4):643–54 e1–9; quiz e39–40.
85. Cai J, Sebastiani G. HIV, elevated transaminases, fatty liver: the perfect storm? J Acquir Immune Defic Syndr. 2019;81(1):e23–e5.
86. Cai J, Osikowicz M, Sebastiani G. Clinical significance of elevated liver transaminases in HIV-infected patients. AIDS. 2019;33(8):1267–82.
87. Allen AM, Therneau TM, Larson JJ, Coward A, Somers VK, Kamath PS. Nonalcoholic fatty liver disease incidence and impact on metabolic burden and death: a 20 year-community study. Hepatology. 2018;67(5):1726–36.
88. Benmassaoud A, Nitulescu R, Pembroke T, Halme AS, Ghali P, Deschenes M, et al. Liver-related events in human immunodeficiency virus-infected persons with occult cirrhosis. Clin Infect Dis. 2019;69(8):1422–30.
89. Akuta N, Kawamura Y, Arase Y, Saitoh S, Fujiyama S, Sezaki H, et al. Hepatocellular carcinoma is the most common liver-related complication in patients with histopathologically-confirmed NAFLD in Japan. BMC Gastroenterol. 2018;18(1):165.
90. Adams LA, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut. 2017;66(6):1138–53.
91. Valenti L, Fracanzani AL, Fargion S. The immunopathogenesis of alcoholic and nonalcoholic steatohepatitis: two triggers for one disease? Semin Immunopathol. 2009;31(3):359–69.
92. Golabi P, Otgonsuren M, Cable R, Felix S, Koenig A, Sayiner M, et al. Non-alcoholic fatty liver disease (NAFLD) is associated with impairment of health related quality of life (HRQOL). Health Qual Life Outcomes. 2016;14:18.
93. Sebastiani G, Alshaalan R, Wong P, Rubino M, Salman A, Metrakos P, et al. Prognostic value of non-invasive fibrosis and steatosis tools, hepatic venous pressure gradient (HVPG) and histology in nonalcoholic steatohepatitis. PLoS One. 2015;10(6):e0128774.
94. Sinn DH, Kang D, Jang HR, Gu S, Cho SJ, Paik SW, et al. Development of chronic kidney disease in patients with non-alcoholic fatty liver disease: a cohort study. J Hepatol. 2017;67(6):1274–80.
95. Petta S, Valenti L, Marchesini G, Di Marco V, Licata A, Camma C, et al. PNPLA3 GG genotype and carotid atherosclerosis in patients with non-alcoholic fatty liver disease. PLoS One. 2013;8(9):e74089.
96. Weinstein G, Zelber-Sagi S, Preis SR, Beiser AS, De Carli C, Speliotes EK, et al. Association of nonalcoholic fatty liver disease with lower brain volume in healthy middle-aged adults in the Framingham Study. JAMA Neurol. 2017.
97. Mantovani A, Byrne CD, Bonora E, Targher G. Nonalcoholic fatty liver disease and risk of incident type 2 diabetes: a meta-analysis. Diabetes Care. 2018;41(2):372–82.
98. Boyd MA, Mocroft A, Ryom L, Monforte AD, Sabin C, El-Sadr WM, et al. Cardiovascular disease (CVD) and chronic kidney disease (CKD) event rates in HIV-positive persons at high predicted CVD and CKD risk: a prospective analysis of the D:A:D observational study. PLoS Med. 2017;14(11):e1002424.
99. Saylor D, Dickens AM, Sacktor N, Haughey N, Slusher B, Pletnikov M, et al. HIV-associated neurocognitive disorder - pathogenesis and prospects for treatment. Nat Rev Neurol. 2016;12(5):309.
100. Triant VA. Cardiovascular disease and HIV infection. Curr HIV/AIDS Rep. 2013;10(3):199–206.
101. Krahn T, Martel M, Sapir-Pichhadze R, Kronfli N, Falutz J, Guaraldi G, et al. Non-alcoholic fatty liver disease predicts development of metabolic comorbidities in HIV-infected patients. J Infect Dis. 2020;222:787–97.
102. Ryom L, Boesecke C, Bracchi M, Ambrosioni J, Pozniak A, Arribas J, et al. Highlights of the 2017 European AIDS Clinical Society (EACS) Guidelines for the treatment of adult HIV-positive persons version 9.0. HIV Med. 2018;19(5):309–15.
103. Sebastiani G, Cocciolillo S, Mazzola G, Malagoli A, Falutz J, Cervo A, et al. Application of guidelines for the management of nonalcoholic fatty liver disease in three prospective cohorts of HIV-monoinfected patients. HIV Med. 2020;21(2):96–108.
104. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology. 2004;40(6):1387–95.
105. Gawrieh S, Wilson LA, Cummings OW, Clark JM, Loomba R, Hameed B, et al. Histologic findings of advanced fibrosis and cirrhosis in patients with nonalcoholic fatty liver disease who have normal aminotransferase levels. Am J Gastroenterol. 2019;114(10):1626–35.
106. Sebastiani G, Gkouvatsos K, Plebani M. Non-invasive assessment of liver fibrosis: it is time for laboratory medicine. Clin Chem Lab Med : CCLM / FESCC. 2011;49(1):13–32.
107. Myers RP, Fong A, Shaheen AA. Utilization rates, complications and costs of percutaneous liver biopsy: a population-based study including 4275 biopsies. Liver Int : official journal of the International Association for the Study of the Liver. 2008;28(5):705–12.
108. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. Hepatology. 2009;49(3):1017–44.
109. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. Gastroenterology. 2019;156(5):1264–81 e4.
110. Price JC, Dodge JL, Ma Y, Scherzer R, Korn N, Tillinghast K, et al. Controlled attenuation parameter and magnetic resonance spectroscopy-measured liver steatosis are discordant in obese HIV-infected adults. AIDS. 2017;31(15):2119–25.
111. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of D, European Association for the Study of O. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402.
112. Morse CG, McLaughlin M, Proschan M, Koh C, Kleiner DE, Heller T, et al. Transient elastography for the detection of hepatic fibrosis in HIV-monoinfected adults with elevated aminotransferases on antiretroviral therapy. AIDS. 2015;29(17):2297–302.
113. Sebastiani G, Alberti A. How far is noninvasive assessment of liver fibrosis from replacing liver biopsy in hepatitis C? J Viral Hepat. 2012;19(Suppl 1):18–32.
114. Sebastiani G. Non-invasive assessment of liver fibrosis in chronic liver diseases: implementation in clinical practice and decisional algorithms. World J Gastroenterol. 2009;15(18):2190–203.
115. Myers RP, Shah H, Burak KW, Cooper C, Feld JJ. An update on the management of chronic hepatitis C: 2015 Consensus

guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol Hepatol. 2015;29(1):19–34.

116.•• Lemoine M, Assoumou L, De Wit S, Girard PM, Valantin MA, Katlama C, et al. Diagnostic accuracy of noninvasive markers of steatosis, NASH, and liver fibrosis in HIV-monoinfected individuals at risk of nonalcoholic fatty liver disease (NAFLD): results from the ECHAM Study. J Acquir Immune Defic Syndr. 2019;80(4):e86–94 **The only study that assessed the accuracy of several non-invasive methods for the diagnosis of NAFLD, NASH, and liver fibrosis in HIV mono-infected patients, using liver histology as the reference.**

117. Kirkegaard-Klitbo DM, Bendtsen F, Lundgren J, Nielsen SD, Benfield T, group Cs. Poor concordance between liver stiffness and noninvasive fibrosis scores in HIV infection without viral hepatitis. Clin Gastroenterol Hepatol. 2019;S1542-3565(19):31169–3.

118. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63(3):743–52.

119. Merchante N, Saroli Palumbo C, Mazzola G, Pineda JA, Tellez F, Rivero-Juarez A, et al. Prediction of esophageal varices by liver stiffness and platelets in persons with HIV infection and compensated advanced chronic liver disease. Clin Infect Dis. 2019.

120. 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.

121. Zelber-Sagi S, Ivancovsky-Wajcman D, Fliss Isakov N, Webb M, Orenstein D, Shibolet O, et al. High red and processed meat consumption is associated with non-alcoholic fatty liver disease and insulin resistance. J Hepatol. 2018;68(6):1239–46.

122. Properzi C, O'Sullivan TA, Sherriff JL, Ching HL, Jeffrey GP, Buckley RF, et al. Ad libitum Mediterranean and low-fat diets both significantly reduce hepatic steatosis: a randomized controlled trial. Hepatology. 2018;68(5):1741–54.

123. Piconi S, Foschi A, Malagoli A, Carli F, Zona S, Milic J, et al. Impact of prolonged maraviroc treatment on non-AIDS-related comorbidities in HIV-positive patients: a retrospective cohort study. J Antimicrob Chemother. 2019;74(9):2723–31.

124. Macias J, Mancebo M, Merino D, Tellez F, Montes-Ramirez ML, Pulido F, et al. Changes in liver steatosis after switching from efavirenz to raltegravir among human immunodeficiency virus-infected patients with nonalcoholic fatty liver disease. Clin Infect Dis. 2017;65(6):1012–9.

125.•• Guaraldi G, Maurice JB, Marzolini C, Monteith K, Milic J, Tsochatzis E, et al. New drugs for NASH and HIV infection: great expectations for a great need. Hepatology. 2020;71(5):1831–44 **This is an opinion paper about pharmacologic treatments for NASH, either already available or under investigation, focused on HIV-infected population. It highlights the aspect of drug–drug interactions with antiretroviral therapy and supports the need for wider inclusion of this population in large trials.**

126. Matthews L, Kleiner DE, Chairez C, McManus M, Nettles MJ, Zemanick K, et al. Pioglitazone for hepatic steatosis in HIV/hepatitis C virus coinfection. AIDS Res Hum Retrovir. 2015;31(10):961–6.

127. Ajmera VH, Cachay E, Ramers C, Vodkin I, Bassirian S, Singh S, et al. MRI assessment of treatment response in HIV-associated NAFLD: a randomized trial of a stearoyl-coenzyme-A-desaturase-1 inhibitor (ARRIVE Trial). Hepatology. 2019;70(5):1531–45.

128.• 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 **This study shows that vitamin E supplementation, administered at the dose recommended in HIV-negative NASH, improves significantly liver transaminases and fatty liver in HIV mono-infected patients with NASH.**

129. 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–e30.

130. Sharma P, McCarty TR, Ngu JN, O'Donnell M, Njei B. Impact of bariatric surgery in patients with HIV infection: a nationwide inpatient sample analysis, 2004-2014. AIDS. 2018;32(14):1959–65.

131. Amouyal C, Buyse M, Lucas-Martini L, Hirt D, Genser L, Torcivia A, et al. Sleeve gastrectomy in morbidly obese HIV patients: focus on anti-retroviral treatment absorption after surgery. Obes Surg. 2018;28(9):2886–93.