A gathering storm: HIV infection and nonalcoholic fatty liver disease in low and middle-income countries

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Despite the decreasing total incidence of liver-related deaths, liver disease remains one of the major non-AIDS causes of morbidity and mortality amongst people living with HIV, and a significant proportion of liver disease in these individuals can be attributed to nonalcoholic fatty liver disease (NAFLD). NAFLD in HIV infection is a growing problem in view of increasing life expectancy associated with the use of effective antiretroviral therapy (ART), wider uptake of ART and increasing rates of obesity in many Asian as well as western countries. The problem may be more pronounced in developing countries where there are limited resources available for mass screening and diagnosis of NAFLD. There is a small but growing body of literature examining NAFLD in the setting of HIV, with data from low and middle-income countries (LMICs) particularly lacking. Here, we review the cohort data on NAFLD in HIV, and discuss the risk factors, pathogenesis of hepatic steatosis, NAFLD and nonalcoholic steatohepatitis (NASH), diagnostic approaches and therapeutic options available for NAFLD in the setting of HIV, and the specific challenges of NAFLD in HIV for LMICs.

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Introduction

Since the introduction of widespread effective HIV antiretroviral therapy (ART), there has been a reduction in the rates of all-cause death, AIDS-related deaths and most non-AIDS related causes of death in people who are HIV-positive [1]. The exception to this trend has been non-AIDS defining cancers in people with viral suppression [1]. Despite decreasing total incidence of liver-related deaths, liver disease remains one of the major non-AIDS causes of morbidity and mortality amongst people living with HIV [1–4]. A significant proportion of the liver disease in these individuals can be attributed to nonalcoholic fatty liver disease (NAFLD), which has been defined as hepatic steatosis without significant alcohol intake (less than 30 g/day for men and 20 g/day for women) or coinfection with such as hepatitis B (HBV) and hepatitis C (HCV) [5–7].

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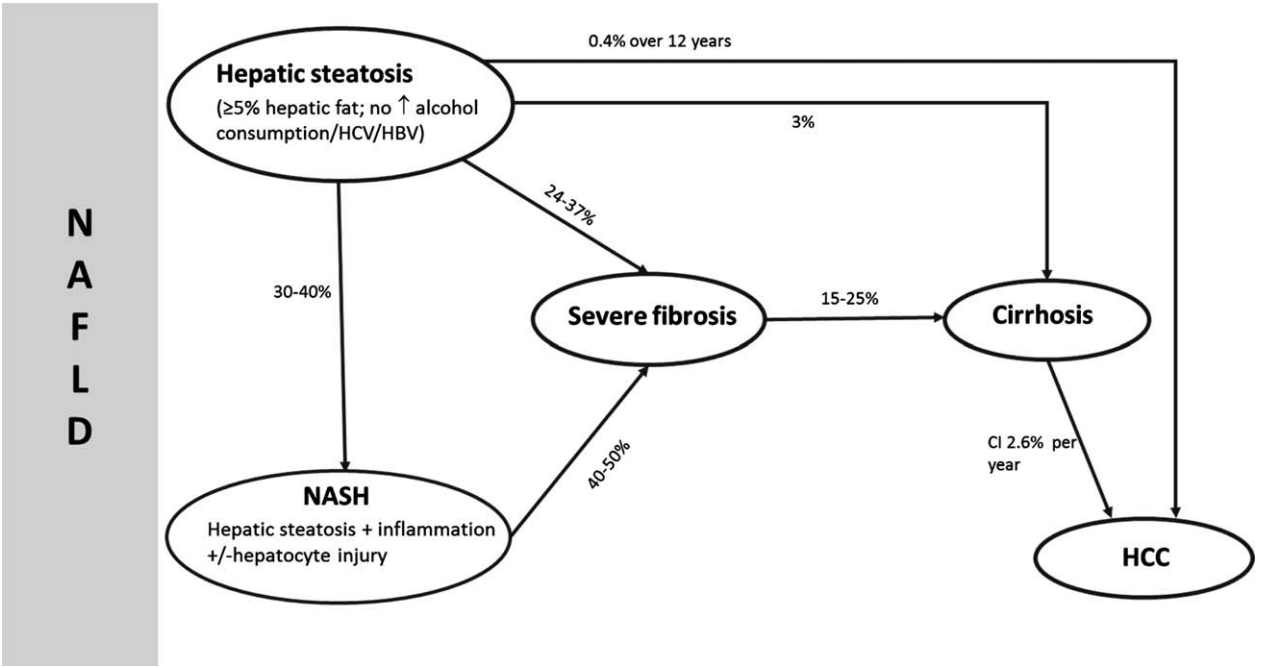

Fig. 1. The disease spectrum of nonalcoholic fatty liver disease in the general population. CI, cumulative incidence; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis. Based on data from [8–12].

The disease spectrum of NAFLD (Fig. 1) [8–12] can range from mild steatosis to an inflammatory state known as nonalcoholic steatohepatitis (NASH), which may progress to cirrhosis, and hepatocellular carcinoma (HCC). NAFLD in HIV infection is a growing problem in view of increasing life expectancy associated with the use of effective ART, wider uptake of ART and increasing rates of obesity in the general population of many Asian as well as western countries. Recent WHO global estimates indicate that many low and middle-income countries (LMICs) are experiencing a rapid surge in obesity and overweight, particularly in urban settings [13]. Although the standard economic term LMIC includes countries with a wide range of ethnic, dietary and cultural differences, cross-sectional data have identified significant proportions of obesity in HIV-positive populations in a range of African countries, India and China [14–16]. Increasing rates of obesity have also been observed in people living with HIV in the United States, Nigeria and the Democratic Republic of Congo [17–19]. The problem may be more pronounced in developing countries where there are limited resources available for mass screening and diagnosis of NAFLD [20]. There is a small but growing body of literature examining NAFLD in the setting of HIV, with data from LMIC particularly lacking.

In this review, we discuss the epidemiology, risk factors, diagnostic approaches and therapeutic options available for NAFLD in the setting of HIV, with a special emphasis on the situation in LMIC.

Pathophysiology: risk factors and natural history

The risk factors that predispose individuals with HIV to NAFLD include traditional risk factors that are also observed in the general population and others, which are more specific to HIV infection. Traditional risk factors include most components of metabolic syndrome (metS) such as obesity, Type 2 diabetes mellitus (T2DM) associated with underlying insulin resistance due to reduced physical activity and overnutrition [21–23], dyslipidaemia and hypertension. When compared with HIV-negative individuals, the risk of having metS is almost double in those with HIV and a prevalence of 15–60% has been reported in some studies. This increased incidence has been observed in both ART-naive and HIV-infected individuals on ART [24,25].

Certain drugs, other than ART, are also responsible for the development of steatohepatitis. Commonly used medications such as amiodarone, methotrexate, tamoxifen, sodium valproate and glucocorticoids are associated with developing fatty liver; the exact pathophysiologic mechanisms, which are multifactorial, are not fully elucidated [26]. It is postulated that not only do these drugs predispose to metS and thereby increase the chances of developing fatty liver, but may also escalate hepatocyte lipogenesis, reduce the secretion of fatty acids and interrupt mitochondrial beta oxidation [26]. The concurrent use of these medications with ART may result in an added risk of developing NAFLD.

HIV-associated risk factors for NAFLD are related to ART and lipodystrophy. Antiretrovirals that precipitate an adverse lipid profile include the nucleotide reverse transcriptase inhibitors (NRTIs); these may indirectly increase the risk of NAFLD via lipid profile alterations. Didanosine (ddI) and stavudine (d4T) are the most commonly implicated NRTI associated with NAFLD; however, their use has been phased out in nearly all treatment guidelines and national programmes [27]. Switching to NRTI-sparing regimens has been associated with an increase in subcutaneous fat and there is some evidence that those on efavirenz (EFV)-based regimens had higher loss of limb fat compared with those on protease inhibitor containing regimens [28]. ART-associated lipodystrophy has primarily occurred with the antiretrovirals ddI, d4T, zidovudine (ZDV) and to a lesser extent EFV [28]; is associated with insulin resistance and dyslipidaemia and is also a major factor driving NAFLD in HIV-infected individuals. Trunk to lower limb fat ratio, as measured using dual-energy X-ray absorptiometry (DEXA), can be used as a surrogate measure of lipodystrophy. In a South Asian HIV cohort receiving ART, a trunk to lower limb fat ratio cut-off more than 2.28 identified lipodystrophy and had the highest odds ratio (OR) for predicting metS, an additional cardiovascular risk [29].

HIV-associated NAFLD seems to be more severe in clinical and biochemical severity. Compared with HIV-uninfected individuals, in the setting of HIV, there is significantly higher liver enzyme and serum triglyceride levels and higher rates of steatohepatitis with more features of liver injury, such as the presence of acidophil bodies and lobular inflammation [30]. Risk factors associated with progression of fibrosis included advancing age, a higher HIV viral load, increased liver enzymes and the use of ddI/d4T [30]. As ddI/d4T are now rarely used, the role of contemporary NRTIs merits further investigation and there is currently insufficient published data for metanalysis of exposure by drug class [31]. Meta-analyses have shown that in the general NAFLD population, those with fibrosis have an increased risk for all-cause mortality and that risk increases with stage of fibrosis [32]. HIV can infect hepatic stellate cells, hepatocytes and Kupffer cells [33,34], and given that significant fibrosis has been observed in treated HIV monoinfection [33,35,36], prospective fibrosis assessment is very important in HIV-NAFLD. In HIV monoinfection, duration of ddI and zidovudine has been associated with cirrhosis, undetectable HIV (<40 copies/ml) with the absence of significant of fibrosis and duration of boosted protease inhibitors had a negative correlation with abnormal liver-stiffness values [35,36].

The pathogenesis of hepatic steatosis, nonalcoholic fatty liver disease and nonalcoholic steatohepatitis

Insulin resistance mediates the increased flux of free fatty acids to hepatocytes from adipose tissue. This induces oxidative stress at the level of the endoplasmic reticulum (ER), promoting steatosis and inflammation. This, coupled with cellular dysfunction, is now referred to as a 'multiple parallel hit model' to explain the development of NASH, which precedes NAFLD [37]. This cellular dysfunction is impacted by the adipocytokines (a range of biologically active mediators generated in adipose tissue) and gut microflora [38]. In obesity, adipocytokines such as interleukin (IL) 6 and tumour necrosis factor-alpha (TNF-α) are elevated, but paradoxically others such as adiponectin are reduced. These alterations have been linked to the development of fatty liver in HIV-negative populations [39]. Recent data have shown that increased adiponectin level is associated with a lower risk of fatty liver regardless of HIV status [39].

The relationship between NAFLD, insulin resistance and visceral fat is complex and not fully understood; however, pro-inflammatory cytokines such as IL-6, C-reactive protein (CRP) and pro-fibrogenics such as fibrinogen may play an important role in this complex interplay [9].

In the setting of HIV infection, increased levels of adiponectin have been associated at the univariate level with lower levels of liver fibrosis, but not when adjusted for MetS [40]. NASH is defined by steatosis, inflammation and hepatocyte damage, and increased bacterial translocation associated with altered gut permeability has been proposed as a trigger for liver inflammation [41]. As HIV infection leads to altered gut permeability and increased bacterial translocation, together with mitochondrial toxicity secondary to NRTIs, this may further add to inflammation in the setting of HIV.

Natural history of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in HIV infection

The early stages of NAFLD usually begin with hepatic steatosis, which is largely benign; however, this may be a forerunner in some individuals to the development of NASH. NASH, when coupled with fibrosis, may in turn lead to more serious consequences such as cirrhosis and, in some, even HCC which can occur in the absence of cirrhosis [21]. Approximately 25–30% of HIV-negative individuals with NAFLD develop NASH [8]. In HIV-positive individuals, however, the severity both at initial presentation and that of progression is higher [30]. Although there are limited data available on histopathological correlation, in a cohort of HIV-positive individuals (91% on ART) with biopsy-proven NAFLD, the prevalence of NASH was 65% and the majority had fibrosis [30].

Coinfection with HCV genotype 3 is also associated with insulin resistance and a higher prevalence of hepatic

steatosis, and it is unclear how effectively this regresses after achieving a sustained virological response [42]. However, with effective treatment now available for HCV, the risk of ongoing inflammation and contribution to development of NAFLD from HCV may reduce over time, although this is dependent on access to directly acting antivirals for HCV which is variable in LMIC [43,44]. In addition, fibrosis associated with HCV does not always resolve, with up to approximately 10% of patients who achieve a sustained virological response after treatment showing persistent or progressive fibrosis [45].

Diagnostic modalities

The diagnostic criteria and therapeutic approach to NAFLD in HIV-positive individuals is the same as for HIV-negative individuals. A range of biochemical and imaging tools have been used both to diagnose NAFLD and to determine the severity, especially in those HIV-positive individuals with metS, lipodystrophy and/or abnormal liver function tests (LFTs). Of the currently available biomarkers/panels, there is no single ideal biomarker that can be used to diagnose NAFLD; however, there are certain noninvasive models utilizing routine clinical parameters that have been proposed to assist diagnosis of steatosis. These are summarised in Table 1 (serum biomarkers) [46–58] and Table 2 (diagnostic/imaging modalities) [59–84].

Current noninvasive diagnostic and imaging techniques have limited success in identifying those individuals with NAFLD who are likely to progress to NASH. The development and validation of reliable, cost-effective and widely available noninvasive biomarkers and imaging techniques for use in clinical care are essential to screen and closely follow individuals with NAFLD to diagnose

Table 1. Range of serum biomarker panels used in the general nonalcoholic fatty liver disease /nonalcoholic steatohepatitis population, worldwide.

Biomarker	Algorithm parameters	Performance	Advantages
SteatoTest [47] (Logistic regression model)	Age, sex, BMI, ALT, α-2 macro globulin, apolipoprotein A1, haptoglobulin, total bilirubin, GGT, cholesterol, serum triglyceride and blood glucose	Diagnosis of steatosis[a], AUROC 0.80 ($n = 884$, training and validation cohort) [47] - Nonbinary AUROC of 0.82 against biopsy scored steatosis[a] ($n = 600$) [48]	Easily available parameters
Fatty Liver Index [49]	BMI, WC, serum triglyceride levels and GGT	Diagnosis of steatosis[a], AUROC 0.97 (95% CI: 0.95–0.98), compared against SteatoTest [50]	Simple algorithm - fewer parameters - validation against MRS [51]
Hepatic Steatosis Index [52]	AST:ALT ratio, BMI and DM	HSI < 30.0 excluded NAFLD with 93.1% (95% CI 92.1–94.1) sensitivity - HSI > 36 detected NAFLD with 93.1% (95% CI 92.0–94.0) specificity	Simple algorithm - minimal blood parameters - developed in a large ($n = 10\,724$) Korean cohort [52] - published data in the setting of HIV [46]
Lipid accumulation product [53], modified to include sex [54]	WC and fasting triglycerides and gender	AUROC 0.78 (IQR 0.72, 0.83) against MRI - in HIV-positive (89% also HCV-positive): LAP > 42 had 74% sensitivity and 89% specificity [55]	Simple algorithm - modified to include sex [54] - validation against MRS [51] - validated in a cohort of HIV-positive individuals [55]
Index of NASH [56]	Triglycerides, ALT, HOMA-IR for women; waist:hip ratio for men only	Cut-off ≥22 had 60% sensitivity and 82% specificity for NAFLD [56] - ≥50 identified NASH from simple steatosis with 92% sensitivity and 60% specificity [56]	Sex-specific - biopsy-proven validation cohort - developed using NHANES III survey - can identify NASH from simple steatosis
Framingham Steatosis Index [57]	Age, sex, BMI, triglycerides, hypertension, DM, and ALT:AST ratio	Cut-off 23 had 71% specificity and 79% sensitivity for hepatic steatosis in the development cohort - AUROC 0.85 (95% CI: 0.84–0.86) against U/S in a large Chinese cohort [58]	Developed using Framingham Third Generation Cohort [57] - published data in a Chinese cohort

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under the receiver operator curve; CI, confidence interval; DM, diabetes mellitus; GGT, gamma glutamyl transferase; HOMA-IR, homeostatic model for assessment for insulin resistance; HSI, hepatic steatosis index; LAP, lipid accumulation product; MRS, H1 magnetic resonance spectroscopy; NHANES III, National Health and Nutrition Examination Survey III; U/S, ultrasound; WC, waist circumference.
[a]Steatosis >5%.

Table 2. Range of diagnostic and imaging modalities used in the general nonalcoholic fatty liver disease/nonalcoholic steatohepatitis population, worldwide.

Diagnostic/Imaging modalities	Sensitivity	Cost	Complications	Patient acceptability	Availability	Comments
Liver biopsy	✓✓✓✓	✓✓✓	✓✓✓	✓	✓✓✓	Gold standard, small area sampled
Ultrasonography [59–62]	✓✓	✓	✓	✓✓✓✓	✓✓✓✓	Most widely used NAFLD screening technique
Hepatorenal ratio [63]	✓✓	✓	✓	✓✓✓✓	✓✓	U/S-based technique
Transient elastography	✓✓	✓	✓	✓✓✓✓	✓✓✓	Used for staging fibrosis in NAFLD, not NAFLD diagnosis
Controlled attenuation parameter [64,65]	✓✓	✓	✓	✓✓✓✓	✓✓	T/E-based technique, also provides fibrosis assessment
Computed tomography [66–68]	✓✓	✓✓	✓✓	✓✓	✓	Radiation exposure
Magnetic resonance spectroscopy and MRI [69–76]	✓✓✓	✓✓✓✓	✓	✓✓	✓	Mostly used in research, published NAFLD data in HIV-positive and in Indian populations
Two-dimensional MR elastography [74,77,78]	✓✓	✓✓✓	✓	✓✓✓	✓	Used for staging fibrosis in NAFLD, not NAFLD diagnosis
Acoustic radiation force impulse elastography [79–84]	✓✓	✓✓✓	✓	✓✓✓	✓	Used for staging fibrosis in NAFLD, not NAFLD diagnosis

Key	Sensitivity/Acceptability/Availability	Cost	Complications
✓	= somewhat	= moderate	= rarely/never
✓✓	= moderately	= expensive	= unlikely, also radiation exposure
✓✓✓	= very good	= very expensive	= possible
✓✓✓✓	= excellent	= extremely expensive	

NASH earlier in the course of the disease and to enable the initiation of life style measures to reduce the risk factors for progression [85]. A combined approach, using the various advantages of different biomarkers/modalities to individual requirements, may provide an efficient way forward.

Cohort studies examining nonalcoholic fatty liver disease in the setting of HIV

To date, there have been more than 30 studies examining NAFLD in the setting of HIV. We have reviewed the 14 studies that all excluded coinfection with HCV and/or HBV as well as excessive alcohol intake (Table 3) [24,30,86–96]. All but one were cross-sectional [46] and cohort size ranged from 14 to 796, with nine studies having cohorts of more than 60 participants. None of these studies were performed in LMICs indicating the significant gap of our understanding of NAFLD in this setting.

Modalities used for the diagnosis of NAFLD/NASH/steatosis varied, including ultrasound, liver biopsy, computed tomography (CT), magnetic resonance spectroscopy (MRS), hepatic steatosis index (HSI) and controlled attenuation parameter (CAP). Reported prevalence of NAFLD and NASH in HIV ranged from 26–65 and 31–72%, respectively. Only two studies reported statistically significant associations between HIV-related factors and NAFLD or NASH after adjustment, which included duration of HIV infection [30] and longer exposure to NRTIs [86]. All other significant associations were non-HIV related, including traditional risk factors that have been identified in the general population: waist circumference [86,87], age [88], lower high-density lipoprotein (HDL) [87], higher triglycerides [87,89], alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ratio and/or ALT [86,90,91], homeostatic model for assessment for insulin resistance [24,88,92,93], higher fasting glucose and insulin [24], male sex [86,88], black ethnicity [46], lower albumin [46], BMI [90,91], visceral adipose tissue (VAT) [92], dyslipidaemia [90], higher APRI and fibrosis-4 scores [30] and γ glutamyl transferase (GGT) [88,93].

Two studies identified associations with metabolic genetic factors. The overexpression of sterol regulatory element binding protein 1 (SREBP-1), involved in the regulation

Table 3. Cohort studies examining nonalcoholic fatty liver disease in the setting of HIV monoinfection that excluded hepatitis B virus, hepatitis C virus and excess alcohol use.

Study	Location, *n*	Female (%)	Age (med)	Med $CD4^+$ cell count	HIV RNA	Duration HIV-positive	ART (%)	Major assessment method	Prevalence of NAFLD/steatosis/ NASH	Associations with NAFLD/steatosis/ NASH[a]
Crum-Cianfione *et al.* [87]	US, *n* = 216	5.6	40	535	50% < 50 copies/ml	10 years	66	U/S	31% NAFLD	NAFLD: waist circumference, TG, HDL ART not significant
Guaraldi *et al.* [86]	Italy, *n* = 255	24.3	48	586[b] 509[c]	2.15 $\log_{10}$ copies/ml[2] 2.23 $\log_{10}$ copies/ml[3]	147.5 months	100	CT	37% NAFLD	NAFLD: ALT:AST ratio, WC, male sex and longer NRTI exposure
Ingiliz *et al.* [24]	France, *n* = 30	3	46	365	200 copies /ml	13 years	100	Liver biopsy	60% steatosis (89% of whom with NASH)	NASH (univariate): fasting glucose, fasting insulin, HOMA ART not significant
Kardashian *et al.* [92]	USA, *n* = 229	35	F: 50 M: 53	F: 569 M: 610	F: 60% U/D M: 86% U/D	N/S	F: 73 M: 97	MRS	F: 17% steatosis M: 41% steatosis	LFF: VAT & HOMA-IR HIV-related factors not significant
Lemoine *et al.* [94]	France, *n* = 33	14.3[c]	43.5[c]	377	50 copies/ml	10.6 years	100	Liver biopsy	57% NASH	Steatosis: expression of SREBP-1
Lombardi *et al.* [88]	Greece, *n* = 125	8	39.5	N/S	333 732 copies/ml	6 years	68	U/S	55% steatosis	Steatosis: male gender, age, HOMA index, GGT ART not significant
Lui *et al.* [89]	Hong Kong, *n* = 240	7	54[c]	503[c]	95% U/D	8yrs[c]	100	MRS	29% FL	FL: TG HIV-related factors not significant
Mohammed *et al.* [96]	Canada, *n* = 51	0	46.2[c]	N/S	N/S	N/S	96	Liver biopsy	Steatosis 35% NASH 65%	-
Morse *et al.* [95]	USA, *n* = 62	6	50	548	<40 copies/ml	17.7 years	100	Liver biopsy	NAFLD 73% NASH 55%	NASH: Insulin resistance, obesity, PNPLA3 gene SNPs HIV-related factors not significant
Nishijima *et al.* [90]	Japan, *n* = 435	7	40	349	52% < 50 copies/ml	N/S	65	U/S	NAFLD 31%	NAFLD: BMI, dyslipidaemia, ALT:AST ratio HIV-related factors not significant
Sebastiani *et al.* [46][d]	Canada, *n* = 796	16	43.5	353.5	40% < 50 copies/ml	years	76	HIS	Steatosis 24% Incidence 6.9 per 100 PY (95% CI 5.9–7.9)	Steatosis: black ethnicity, albumin
Sterling *et al.* [93]	USA, *n* = 14	29	45	614	100% < 50 copies/ml	N/S	100	Liver biopsy	Steatosis 65% NASH 26%	Steatosis: GGT NASH: HOMA-IR
Vodkin *et al.* [30]	USA, *n* = 66	21.2	44.8[c]	612.5	78.8% < 400 copies/ml	118.4 m	91	Liver biopsy	64% NASH HIV-positive	NAFLD: APRI, FIB-4 NASH: duration of HIV
Vuille-Lessard *et al.* [91]	Canada, *n* = 300	23.3	51.5[a] 49[b]	N/S	92.4%[b] 87.83[c] <40 copies /ml	13 years[b] 11 years[c]	88[b] 90[c]	CAP	48% NAFLD	NAFLD: BMI, ALT

ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; ART, antiretroviral therapy; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; CI, confidence interval; CT, computed tomography; F, female; F/L, fatty liver; FIB-4, fibrosis 4 score; GGT, γ-glutamyl transpeptidase; HDL, high-density lipoprotein; HOMA-IR, homeostatic model for assessment of insulin resistance; HSI, hepatic steatosis index; LFF, liver fat fraction; M, male; MRS, magnetic resonance spectroscopy; MVA, multivariable analysis; N/S, not stated; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; PY, person-years; SNP, single-nucleotide polymorphisms; SREBP-1, sterol regulatory element binding protein 1; T/E, transient elastography; TG, triglyceride; U/D, undetectable; U/S, ultrasound; VAT, visceral adipose tissue; WC, waist circumference.

[a]Multivariate analyses unless otherwise stated.

[b]Subgroup with NAFLD.

[c]Subgroup without NAFLD.

[d]The only retrospective longitudinal study. All other studies are cross-sectional.

of lipid metabolism, was associated with steatosis [94] and the presence of single-nucleotide polymorphisms in the gene coding for patatin-like phospholipase domain-containing 3 protein (PNPLA3) was associated with NASH [95]. However, these polymorphisms are general risk factors and not HIV-specific.

Although all 14 study cohorts had a lower proportion of women participants (0–29%) than men, male sex was reported as a risk factor in two cohorts (24 and 8% women [86,88]). One cohort (35% women) presented major analyses by sex [92]. They reported that although HIV-infected women (73% on ART) had a higher liver fat fraction (LFF) than HIV-negative women, LFF was similar in HIV-positive (97% on ART) and HIV-negative men. LFF was defined as the ratio of total lipids to total lipids and unsuppressed water, as measured by MRS and expressed as a percentage. There was less VAT in women than men, and HIV-infected women had 25% less LFF than HIV-infected men.

Only one published study to date has examined hepatic steatosis longitudinally; however, although the cohort was large ($n = 796$), the study was retrospective and diagnosed steatosis using the HSI [46]. Median follow-up was 4.9 years and they found an incidence of steatosis of 6.9/100 person-years [95% confidence interval (95% CI) 5.9–7.9]. They reported associations between development of hepatic steatosis with black ethnicity and lower albumin, in adjusted models.

A recent systematic review and meta-analysis examined 10 of these studies and reported a prevalence of NAFLD and NASH in the setting of HIV of 35% (95% CI 29–42) and 42% (95% CI 22–64), respectively [31]. Although the key risk for factors for NAFLD were related to metS (BMI, waist circumference, T2DM, hypertension and triglycerides), they did report an association between NAFLD and higher $CD4^+$ cell count [mean difference of 54.83 (95% CI 11.55–98.11, $P = 0.0$)], based on data from four studies [86,87,89,90].

Although NAFLD is more prevalent in HIV than in the general population, studies in HIV monoinfection cohorts to date have not consistently found statistically significant associations with HIV-related factors. This may likely be due to the limited numbers of studies that have investigated NAFLD in HIV and excluded viral hepatitis/excess alcohol, and the diversity in the cohorts. There is an obvious need for prospective longitudinal studies sufficiently powered to robust outcomes.

Treatment for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis

Currently available options

There are no treatments for NAFLD or NASH that are specific to people living with HIV. Currently, lifestyle modification and dietary changes are the main interventions for NAFLD, in conjunction with the specific treatment of associated metabolic disorders. A multidisciplinary team approach is beneficial to manage such cases [97].

Lifestyle changes including weight loss achieved by both dietary changes and enhanced physical exercise remain the first line of treatment [98]. Weight loss of about 3–5% of body weight is recommended to improve steatosis and about 10% to improve histological features of NASH, including portal inflammation and fibrosis [98].

Pharmacologic therapy is currently offered only to those with NASH, and in particular those with NASH and significant fibrosis. Current European guidelines suggest the use of glitazones or Vitamin E, or in combination [99]. There are no drugs to date that have completed phase III trials and none approved for NASH by regulatory authorities [99]. The underlying risk factors should be managed as per the standard of care for individual disorders [100].

Approaches in development

There are several new agents in development in the drug pipeline. Of interest in HIV-NAFLD is cenicriviroc (CVC), a chemokine receptor type 5 (CCR5) and chemokine receptor type 2 (CCR2) antagonist that has anti-HIV activity both *in vitro* and *in vivo* [101,102]. CCR2 plays a critical role in recruiting monocytes with an inflammatory phenotype into the liver, while CCR5 attracts lymphocytes into the liver and is directly involved in fibrogenic activation of hepatic stellate cells [103]. In addition, CVC has been shown to reduce circulating markers of monocyte inflammation in HIV-infected individuals on ART, including soluble CD14 [102]. In a large randomized phase 2b study of CVC in HIV-negative individuals with NASH (CENTAUR), CVC resulted in a reduction in multiple markers of inflammation, including IL1b, high-sensitivity CCRP, IL6 and fibrinogen [104]. In addition, a reduction in soluble (s)CD14 and increase in the ligands for CCR2 (CCL2) and CCR5 (CCL3 and 4) was observed. These changes in chemokine activity reduce inflammation and fibrotic activity, which was, most importantly, observed clinically in this study with a significant decline in hepatic fibrosis [104]. CVC is now in Phase 3 clinical trials and is not yet approved.

Specific challenges in low and middle-income countries

Most LMIC ART programmes routinely offer TDF-based therapy as first-line treatment due to toxicity associated with ddI, d4T and zidovudine. However, the availability of newer NRTIs, such as TAF and abacavir-based regimens, is still out of reach for many in LMIC due

to cost. In addition, most government programmes do not currently have any defined guidelines to detect ongoing liver inflammation. Most liver dysfunction is diagnosed either incidentally by assessment of LFTs (often in the stage of steatohepatitis) or on presentation with decompensated liver disease. Cost-effective screening algorithms for LMICs based on sound scientific data are needed to screen for NAFLD-related disorders.

In India specifically, as South Asians have higher total body fat for a given BMI than western populations, including at normal range BMI [105,106], healthy BMI may not be indicative of total body fat in this population. Rates of metS and insulin resistance are high in Asian populations, and in particular in South Asia [107]. There are limited published studies with data from HIV-infected cohorts, including Japan [90], China [89] and Thailand [108]. Data in HIV-infection from Japan and China have shown an incidence of NALFD among HIV-infected individuals of Asian origin similar to that observed in western countries, and an association with conventional NAFLD-related risk factors. However, the Thai data (retrospective study of HIV-positive forensic autopsies from one hospital) reported that only 7.5% showed fatty change of the liver [108]. Data from the Indian subcontinent are sparse and mainly confined to autopsy in the general population, where in one study 9.2% of the cohort was HIV positive [109]. Data from African countries are not uniform, with both a lower prevalence than in whites reported in HIV-infected individuals on ART (range 6–42 months) in Nigeria [110], while a similar prevalence to that in the West was reported in HIV-infected individuals on ART (minimum 6 months) in Cameroon [111]. There is a great need for prospective cohort studies generating data in LMICs, which would then lead to specific policies and guidelines, tailored to these countries [112,113].

Management and monitoring of NAFLD in HIV-infected individuals, particularly in LMIC where there is increased visceral fat in the healthy weight range, increasing levels of obesity and prediabetes combined with large numbers of people living with HIV, could be a very significant health burden that requires management and prevention strategies. Screening individuals newly diagnosed with HIV using a cost-effective and widely available modality such as liver ultrasound would be beneficial, although effective treatment options for NAFLD beyond modification of lifestyle factors remain elusive. An initial focus on monitoring those diagnosed with NAFLD in the setting of HIV in LMICs would be useful, particularly tracking fibrosis progression with T/E or CAP to identify those at risk of NASH and/or HCC.

Conclusion

Although there is a small but growing body of literature on HIV-associated NAFLD, there are still large gaps regarding the optimal guidelines for NAFLD screening and management in the setting of HIV, particularly in LMIC. Guidelines in those who are HIV-infected may need to differ from the HIV-negative population, as NAFLD prevalence in the setting of HIV appears higher, progression to NASH more frequent and a role for HIV-related factors has not been fully elucidated. Importantly, there are no data to date prospectively examining NAFLD progression in HIV-positive individuals and very little published from LMIC and in HIV-infected women. Further research is also required to develop noninvasive markers for diagnosis and monitoring of NAFLD and its progression to NASH to identify those at highest risk for advanced liver disease. An increased role of genetic testing for predicting progression and new therapeutic interventions could potentially play a role in the future.

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Conflicts of interest

There are no conflicts of interest.

References

1. 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**:241–248.
2. Eyawo O, Franco-Villalobos C, Hull MW, Nohpal A, Samji H, Sereda P, *et al*. **Changes in mortality rates and causes of death in a population-based cohort of persons living with and without HIV from 1996 to 2012.** *BMC Infect Dis* 2017; **17**:174.
3. Smith C, Sabin CA, Lundgren JD, Thiebaut R, Weber R, Law M, *et al*. **Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study.** *AIDS* 2010; **24**:1537–1548.

4. Weber R, Ruppik M, Rickenbach M, Spoerri A, Furrer H, Battegay M, *et al*. **Decreasing mortality and changing patterns of causes of death in the Swiss HIV Cohort Study.** *HIV Med* 2013; **14**:195–207.
5. Lemoine M, Serfaty L, Capeau J. **From nonalcoholic fatty liver to nonalcoholic steatohepatitis and cirrhosis in HIV-infected patients: diagnosis and management.** *Curr Opin Infect Dis* 2012; **25**:10–16.
6. Sanyal AJ, Brunt EM, Kleiner DE, Kowdley KV, Chalasani N, Lavine JE, *et al*. **Endpoints and clinical trial design for nonalcoholic steatohepatitis.** *Hepatology* 2011; **54**:344–353.
7. The Antiretroviral Therapy Cohort C. **Causes of death in HIV-1–infected patients treated with antiretroviral therapy, 1996–2006: collaborative analysis of 13 HIV cohort studies.** *Clin Infect Dis* 2010; **50**:1387–1396.
8. McCullough AJ. **Pathophysiology of nonalcoholic steatohepatitis.** *J Clin Gastroenterol* 2006; **40 (Suppl 1)**:S17–S29.
9. Byrne CD, Targher G. **NAFLD: a multisystem disease.** *J Hepatol* 2015; **62 (Suppl 1)**:S47–S64.
10. Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. **The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis.** *Hepatology* 2010; **51**:1972–1978.
11. Kawamura Y, Arase Y, Ikeda K, Seko Y, Imai N, Hosaka T, *et al*. **Large-scale long-term follow-up study of Japanese patients with non-alcoholic fatty liver disease for the onset of hepatocellular carcinoma.** *Am J Gastroenterol* 2011; **107**:253–261.
12. McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. **Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management.** *J Hepatol* 2015; **62**:1148–1155.
13. World Health Organization. Obesity and overweight: fact sheet. 2018. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. [Accessed 20 November 2018]
14. Bijker R, Choi JY, Ditangco R, Kiertiburanakul S, Lee MP, Siwamogsatham S, *et al*. **Cardiovascular disease and cardiovascular disease risk in HIV-positive populations in the Asian region.** *Open AIDS J* 2017; **11**:52–66.
15. Mashinya F, Alberts M, Colebunders R, Van Geertruyden JP. **Weight status and associated factors among HIV infected people on antiretroviral therapy in rural Dikgale, Limpopo, South Africa.** *Afr J Prim Health Care Fam Med* 2016; **8**:e1–e8.
16. Semu H, Zack RM, Liu E, Hertzmark E, Spiegelman D, Sztam K, *et al*. **Prevalence and risk factors for overweight and obesity among HIV-infected adults in Dar es Salaam, Tanzania.** *J Int Assoc Provid AIDS Care* 2016; **15**:512–521.
17. 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**:e10106.
18. Ezechi LO, Musa ZA, Otobo VO, Idigbe IE, Ezechi OC. **Trends and risk factors for obesity among HIV positive Nigerians on antiretroviral therapy.** *Ceylon Med J* 2016; **61**:56–62.
19. Mandina Ndona M, Longo-Mbenza B, Wumba R, Tandu Umba B, Buassa-Bu-Tsumbu B, Mbula Mambimbi M, *et al*. **Nadir CD4+, religion, antiretroviral therapy, incidence of type 2 diabetes mellitus, and increasing rates of obesity among black Africans with HIV disease.** *Int J Gen Med* 2012; **5**:983–990.
20. Ahmed MH, Noor SK, Bushara SO, Husain NE, Elmadhoun WM, Ginawi IA, *et al*. **Non-alcoholic fatty liver disease in Africa and middle east: an attempt to predict the present and future implications on the healthcare system.** *Gastroenterol Res* 2017; **10**:271–279.
21. Angulo P. **GI epidemiology: nonalcoholic fatty liver disease.** *Aliment Pharmacol Ther* 2007; **25**:883–889.
22. Bonfanti P, Giannattasio C, Ricci E, Facchetti R, Rosella E, Franzetti M, *et al*. **HIV and metabolic syndrome: a comparison with the general population.** *J Acquir Immune Defic Syndr* 2007; **45**:426–431.
23. Grunfeld C. **Insulin resistance in HIV infection: drugs, host responses, or restoration to health?** *Topics HIV Med* 2008; **16**:89–93.
24. Ingiliz P, Valantin M-A, Duvivier C, Medja F, Dominguez S, Charlotte F, *et al*. **Liver damage underlying unexplained transaminase elevation in human immunodeficiency virus-1 monoinfected patients on antiretroviral therapy.** *Hepatology* 2009; **49**:436–442.
25. 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.
26. Rabinowich L, Shibolet O. **Drug induced steatohepatitis: an uncommon culprit of a common disease.** *BioMed Res Int* 2015; **2015**:168905.
27. Blanco F, Barreiro P, Ryan P, Vispo E, Martín-Carbonero L, Tuma P, *et al*. **Risk factors for advanced liver fibrosis in HIV-infected individuals: role of antiretroviral drugs and insulin resistance.** *J Viral Hepat* 2011; **18**:11–16.
28. de Waal R, Cohen K, Maartens G. **Systematic review of antiretroviral-associated lipodystrophy: lipoatrophy, but not central fat gain, is an antiretroviral adverse drug reaction.** *PLoS One* 2013; **8**:e63623.
29. Asha HS, Seshadri MS, Paul TV, Abraham OC, Rupali P, Thomas N. **Human immunodeficiency virus-associated lipodystrophy: an objective definition based on dual-energy x-ray absorptiometry-derived regional fat ratios in a South Asian population.** *Endocr Pract* 2012; **18**:158–169.
30. Vodkin I, Valasek MA, Bettencourt R, Cachay E, Loomba R. **Clinical, biochemical and histological differences between HIV-associated NAFLD and primary NAFLD: a case-control study.** *Aliment Pharmacol Ther* 2015; **41**:368–378.
31. 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**:1621–1632.
32. 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**:1557–1565.
33. Mohr R, Schierwagen R, Schwarze-Zander C, Boesecke C, Wasmuth JC, Trebicka J, *et al*. **Liver fibrosis in HIV patients receiving a modern cART: which factors play a role?** *Medicine (Baltimore)* 2015; **94**:e2127.
34. Singh KP, Crane M, Audsley J, Avihingsanon A, Sasadeusz J, Lewin SR. **HIV-hepatitis B virus coinfection: epidemiology, pathogenesis, and treatment.** *AIDS* 2017; **31**:2035–2052.
35. Anadol E, Lust K, Boesecke C, Schwarze-Zander C, Mohr R, Wasmuth JC, *et al*. **Exposure to previous cART is associated with significant liver fibrosis and cirrhosis in human immunodeficiency virus-infected patients.** *PLoS One* 2018; **13**:e0191118.
36. Han SH, Kim SU, Kim CO, Jeong SJ, Park JY, Choi JY, *et al*. **Abnormal liver stiffness assessed using transient elastography (Fibroscan®) in HIV-infected patients without HBV/HCV coinfection receiving combined antiretroviral treatment.** *PLoS One* **2013; 8:e52720**.
37. Tilg H, Moschen AR. **Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis.** *Hepatology* 2010; **52**:1836–1846.
38. Stojsavljevic S, Gomercic Palcic M, Virovic Jukic L, Smircic Duvnjak L, Duvnjak M. **Adipokines and proinflammatory cytokines, the key mediators in the pathogenesis of nonalcoholic fatty liver disease.** *World J Gastroenterol* 2014; **20**:18070–18091.
39. Price JC, Wang R, Seaberg EC, Budoff MJ, Kingsley LA, Palella FJ, *et al*. **The association of inflammatory markers with nonalcoholic fatty liver disease differs by human immunodeficiency virus serostatus.** *Open Forum Infect Dis* 2017; **4**:ofx153.
40. 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.** *AIDS* 2017; **31**:1955–1964.
41. Schuster S, Cabrera D, Arrese M, Feldstein AE. **Triggering and resolution of inflammation in NASH.** *Nat Rev Gastroenterol Hepatol* 2018; **15**:349–364.
42. McGovern Barbara H, Ditelberg Jeremy S, Taylor Lynn E, Gandhi Rajesh T, Christopoulos Katerina A, Chapman S, *et al*. **Hepatic steatosis is associated with fibrosis, nucleoside analogue use, and hepatitis C virus genotype 3 infection in HIV-seropositive patients.** *Clin Infect Dis* 2006; **43**:365–372.
43. Ford N, Wiktor S, Kaplan K, Andrieux-Meyer I, Hill A, Radhakrishnan P, *et al*. **Ten priorities for expanding access to HCV treatment for people who inject drugs in low- and middle-income countries.** *Int J Drug Policy* 2015; **26**:1088–1093.
44. Walsh N, Durier N, Khwairakpam G, Sohn AH, Lo YR. **The hepatitis C treatment revolution: how to avoid Asia missing out.** *J Virus Erad* 2015; **1**:272–275.

45. Lee YA, Wallace MC, Friedman SL. **Pathobiology of liver fibrosis: a translational success story.** *Gut* 2015; **64**:830–841.
46. 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 Dis* 2015; **2**:ofv015.
47. Poynard T, Ratziu V, Naveau S, Thabut D, Charlotte F, Messous D, *et al*. **The diagnostic value of biomarkers (SteatoTest) for the prediction of liver steatosis.** *Comp Hepatol* 2005; **4**:10.
48. Munteanu M, Tiniakos D, Anstee Q, Charlotte F, Marchesini G, Bugianesi E, *et al*. **Diagnostic performance of FibroTest, SteatoTest and ActiTest in patients with NAFLD using the SAF score as histological reference.** *Aliment Pharmacol Ther* 2016; **44**:877–889.
49. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, *et al*. **The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population.** *BMC Gastroenterol* 2006; **6**:33.
50. Zelber-Sagi S, Webb M, Assy N, Blendis L, Yeshua H, Leshno M, *et al*. **Comparison of fatty liver index with noninvasive methods for steatosis detection and quantification.** *World J Gastroenterol* 2013; **19**:57–64.
51. Cuthbertson DJ, Weickert MO, Lythgoe D, Sprung VS, Dobson R, Shoajee-Moradie F, *et al*. **External validation of the fatty liver index and lipid accumulation product indices, using 1H-magnetic resonance spectroscopy, to identify hepatic steatosis in healthy controls and obese, insulin-resistant individuals.** *Eur J Endocrinol* 2014; **171**:561–569.
52. Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, *et al*. **Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease.** *Dig Liver Dis* 2010; **42**:503–508.
53. Kahn HS. **The 'lipid accumulation product' performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison.** *BMC Cardiovasc Disord* 2005; **5**:26.
54. Bedogni G, Kahn HS, Bellentani S, Tiribelli C. **A simple index of lipid overaccumulation is a good marker of liver steatosis.** *BMC Gastroenterol* 2010; **10**:98.
55. Siddiqui MS, Patidar KR, Boyett S, Smith PG, Sanyal AJ, Sterling RK. **Validation of noninvasive methods for detecting hepatic steatosis in patients with human immunodeficiency virus infection.** *Clin Gastroenterol Hepatol* 2015; **13**:402–405.
56. Otgonsuren M, Estep MJ, Hossain N, Younossi E, Frost S, Henry L, *et al*. **Single noninvasive model to diagnose nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH).** *J Gastroenterol Hepatol* 2014; **29**:2006–2013.
57. Long MT, Pedley A, Colantonio LD, Massaro JM, Hoffmann U, Muntner P, *et al*. **Development and validation of the Framingham steatosis index to identify persons with hepatic steatosis.** *Clin Gastroenterol Hepatol* 2016; **14**:1172–1180e1172.
58. Shen YN, Yu MX, Gao Q, Li YY, Huang JJ, Sun CM, *et al*. **External validation of noninvasive prediction models for identifying ultrasonography-diagnosed fatty liver disease in a Chinese population.** *Medicine* 2017; **96**:e7610.
59. Jimba S, Nakagami T, Takahashi M, Wakamatsu T, Hirota Y, Iwamoto Y, *et al*. **Prevalence of nonalcoholic fatty liver disease and its association with impaired glucose metabolism in Japanese adults.** *Diabet Med* 2005; **22**:1141–1145.
60. Lee DH. **Imaging evaluation of nonalcoholic fatty liver disease: focused on quantification.** *Clin Mol Hepatol* 2017; **23**:290–301.
61. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, *et al*. **The utility of radiological imaging in nonalcoholic fatty liver disease.** *Gastroenterology* 2002; **123**:745–750.
62. Wu J, You J, Yerian L, Shiba A, Schauer PR, Sessler DI. **Prevalence of liver steatosis and fibrosis and the diagnostic accuracy of ultrasound in bariatric surgery patients.** *Obes Surg* 2012; **22**:240–247.
63. Borges VF, Diniz AL, Cotrim HP, Rocha HL, Andrade NB. **Sonographic hepatorenal ratio: a noninvasive method to diagnose nonalcoholic steatosis.** *J Clin Ultrasound* 2013; **41**:18–25.
64. de Ledinghen V, Hiriart JB, Vergniol J, Merrouche W, Bedossa P, Paradis V. **Controlled attenuation parameter (CAP) with the XL probe of the fibroscan((R)): a comparative study with the M probe and liver biopsy.** *Dig Dis Sci* 2017; **62**:2569–2577.
65. Shi KQ, Tang JZ, Zhu XL, Ying L, Li DW, Gao J, *et al*. **Controlled attenuation parameter for the detection of steatosis severity in chronic liver disease: a meta-analysis of diagnostic accuracy.** *J Gastroenterol Hepatol* 2014; **29**:1149–1158.
66. Fierbinteanu-Braticevici C, Dina I, Petrisor A, Tribus L, Negreanu L, Carstoiu C. **Noninvasive investigations for non alcoholic fatty liver disease and liver fibrosis.** *World J Gastroenterol* 2010; **16**:4784–4791.
67. Johnston RJ, Stamm ER, Lewin JM, Hendrick RE, Archer PG. **Diagnosis of fatty infiltration of the liver on contrast enhanced CT: limitations of liver-minus-spleen attenuation difference measurements.** *Abdom Imaging* 1998; **23**:409–415.
68. Kinner S, Reeder SB, Yokoo T. **Quantitative imaging biomarkers of NAFLD.** *Dig Dis Sci* 2016; **61**:1337–1347.
69. Bohte AE, van Werven JR, Bipat S, Stoker J. **The diagnostic accuracy of US, CT, MRI and 1H-MRS for the evaluation of hepatic steatosis compared with liver biopsy: a meta-analysis.** *Eur Radiol* 2011; **21**:87–97.
70. Livingstone RS, Grunnet LG, Thomas N, Eapen A, Antonisamy B, Mohan VR, *et al*. **Are hepatic and soleus lipid content, assessed by magnetic resonance spectroscopy, associated with low birth weight or insulin resistance in a rural Indian population of healthy young men?** *Diabet Med* 2016; **33**:365–370.
71. Middleton MS, Heba ER, Hooker CA, Bashir MR, Fowler KJ, Sandrasegaran K, *et al*. **Agreement between magnetic resonance imaging proton density fat fraction measurements and pathologist-assigned steatosis grades of liver biopsies from adults with nonalcoholic steatohepatitis.** *Gastroenterology* 2017; **153**:753–761.
72. Moreno-Torres A, Domingo P, Pujol J, Blanco-Vaca F, Arroyo JA, Sambeat MA. **Liver triglyceride content in HIV-1-infected patients on combination antiretroviral therapy studied with 1H-MR spectroscopy.** *Antiviral Ther* 2007; **12**:195–203.
73. Nasr P, Forsgren MF, Ignatova S, Dahlstrom N, Cedersund G, Leinhard OD, *et al*. **Using a 3% proton density fat fraction as a cut-off value increases sensitivity of detection of hepatic steatosis, based on results from histopathology analysis.** *Gastroenterology* 2017; **153**:53–55e57.
74. Park CC, Nguyen P, Hernandez C, Bettencourt R, Ramirez K, Fortney L, *et al*. **Magnetic resonance elastography vs transient elastography in detection of fibrosis and noninvasive measurement of steatosis in patients with biopsy-proven nonalcoholic fatty liver disease.** *Gastroenterology* 2017; **152**:598–607e592.
75. Qayyum A. **MR spectroscopy of the liver: principles and clinical applications.** *Radiographics* 2009; **29**:1653–1664.
76. Thomas EL, Fitzpatrick JA, Malik SJ, Taylor-Robinson SD, Bell JD. **Whole body fat: content and distribution.** *Prog Nucl Magn Reson Spectrosc* 2013; **73**:56–80.
77. Loomba R, Sirlin CB, Ang B, Bettencourt R, Jain R, Salotti J, *et al*. **Ezetimibe for the treatment of nonalcoholic steatohepatitis: assessment by novel magnetic resonance imaging and magnetic resonance elastography in a randomized trial (MOZART trial).** *Hepatology* 2015; **61**:1239–1250.
78. Loomba R, Wolfson T, Ang B, Hooker J, Behling C, Peterson M, *et al*. **Magnetic resonance elastography predicts advanced fibrosis in patients with nonalcoholic fatty liver disease: a prospective study.** *Hepatology* 2014; **60**:1920–1928.
79. Cassinotto C, Boursier J, de Ledinghen V, Lebigot J, Lapuyade B, Cales P, *et al*. **Liver stiffness in nonalcoholic fatty liver disease: a comparison of supersonic shear imaging, FibroScan, and ARFI with liver biopsy.** *Hepatology* 2016; **63**:1817–1827.
80. Cui J, Heba E, Hernandez C, Haufe W, Hooker J, Andre MP, *et al*. **MRE is superior to ARFI for the diagnosis of fibrosis in patients with biopsy-proven NAFLD: a prospective study.** *Hepatology* 2016; **63**:453–461.
81. Liu H, Fu J, Hong R, Liu L, Li F. **Acoustic radiation force impulse elastography for the non-invasive evaluation of hepatic fibrosis in non-alcoholic fatty liver disease patients: a systematic review & meta-analysis.** *PLoS One* 2015; **10**:e0127782.
82. Palmeri ML, Wang MH, Dahl JJ, Frinkley KD, Nightingale KR. **Quantifying hepatic shear modulus in vivo using acoustic radiation force.** *Ultrasound Med Biol* 2008; **34**:546–558.
83. Palmeri ML, Wang MH, Rouze NC, Abdelmalek MF, Guy CD, Moser B, *et al*. **Noninvasive evaluation of hepatic fibrosis using acoustic radiation force-based shear stiffness in patients with nonalcoholic fatty liver disease.** *J Hepatol* 2011; **55**:666–672.

84. Yoneda M, Suzuki K, Kato S, Fujita K, Nozaki Y, Hosono K, *et al*. **Nonalcoholic fatty liver disease: US-based acoustic radiation force impulse elastography.** *Radiology* 2010; **256**:640–647.
85. Loomba R, Abraham M, Unalp A, Wilson L, Lavine J, Doo E, *et al*. **Association between diabetes, family history of diabetes, and risk of nonalcoholic steatohepatitis and fibrosis.** *Hepatology* 2012; **56**:943–951.
86. 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**:250–257.
87. 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* 2009; **50**:464–473.
88. 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**:1471–1477.
89. 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**:411–421.
90. 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**:e87596.
91. 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**:2635–2643.
92. 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* 2017; **31**:365–373.
93. Sterling RK, Smith PG, Brunt EM. **Hepatic steatosis in human immunodeficiency virus: a prospective study in patients without viral hepatitis, diabetes, or alcohol abuse.** *J Clin Gastroenterol* 2013; **47**:182–187.
94. Lemoine M, Barbu V, Girard PM, Kim M, Bastard JP, Wendum D, *et al*. **Altered hepatic expression of SREBP-1 and PPAR-gamma is associated with liver injury in insulin-resistant lipodystrophic HIV-infected patients.** *AIDS* 2006; **20**:387–395.
95. 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**:1569–1578.
96. Mohammed SS, Aghdassi E, Salit IE, Avand G, Sherman M, Guindi M, *et al*. **HIV-positive patients with nonalcoholic fatty liver disease have a lower body mass index and are more physically active than HIV-negative patients.** *JAIDS* 2007; **45**:432–438.
97. Loria P, Adinolfi LE, Bellentani S, Bugianesi E, Grieco A, Fargion S, *et al*. **Practice guidelines for the diagnosis and management of nonalcoholic fatty liver disease. A decalogue from the Italian Association for the Study of the Liver (AISF) Expert Committee.** *Dig Liver Dis* 2010; **42**:272–282.
98. 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**:328–357.
99. **EASL–EASD–EASO Clinical Practice Guidelines for the management of nonalcoholic fatty liver disease.** *J Hepatol* 2016; **64**:1388–1402.
100. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, *et al*. **The diagnosis and management of nonalcoholic 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**:2005–2023.
101. Klibanov OM, Williams SH, Iler CA. **Cenicriviroc, an orally active CCR5 antagonist for the potential treatment of HIV infection.** *Curr Opin Investig Drugs* 2010; **11**:940–950.
102. Thompson M, Saag M, DeJesus E, Gathe J, Lalezari J, Landay AL, *et al*. **A 48-week randomized phase 2b study evaluating cenicriviroc versus efavirenz in treatment-naive HIV-infected adults with C-C chemokine receptor type 5-tropic virus.** *AIDS* 2016; **30**:869–878.
103. Tacke F. **Cenicriviroc for the treatment of nonalcoholic steatohepatitis and liver fibrosis.** *Expert Opin Investig Drugs* 2018; **27**:301–311.
104. Friedman SL, Ratziu V, Harrison SA, Abdelmalek MF, Aithal GP, Caballeria J, *et al*. **A randomized, placebo-controlled trial of cenicriviroc for treatment of nonalcoholic steatohepatitis with fibrosis.** *Hepatology* 2018; **67**:1754–1767.
105. Kesavachandran C, Bihari V, Mathur N. **The normal range of body mass index with high body fat percentage among male residents of Lucknow city in north India.** *Indian J Med Res* 2012; **135**:72–77.
106. Shah A, Kanaya AM. **Diabetes and associated complications in the South Asian population.** *Curr Cardiol Rep* 2014; **16**:476.
107. Ramachandran A, Wan Ma RC, Snehalatha C. **Diabetes in Asia.** *Lancet* 2010; **375**:408–418.
108. Peonim V, Sujirachato K, Srisont S, Udnoon J. **Pathology of HIV seropositive: forensic autopsy study in a tertiary care hospital, Bangkok, Thailand.** *J Med Assoc Thai* 2012; **95**:1059–1065.
109. Amarapurkar A, Ghansar T. **Fatty liver: experience from western India.** *Ann Hepatol* 2007; **6**:37–40.
110. Lesi OA, Soyebi KS, Eboh CN. **Fatty liver and hyperlipidemia in a cohort of HIV-positive Africans on highly active antiretroviral therapy.** *J Natl Med Assoc* 2009; **101**:151–155.
111. Ongolo-Zogo P, Nkodo Mbia N, Mvogo Minkala TL, Biwole Sida M, Kouanfack C, Nko Amvene S. **[Lipodystrophy and echographic hepatic steatosis in HIV-positive patients under highly active antiretroviral therapy (HAART) in Yaounde (Cameroon)].** *Bull Soc Pathol Exot* 19902012; **105**:353–360.
112. Kelly P, Saloojee H, Chen JY, Chung RT. **Noncommunicable diseases in HIV infection in low- and middle-income countries: gastrointestinal, hepatic, and nutritional aspects.** *J Acquir Immune Defic Syndr* 2014; **67 (Suppl 1)**:S79–S86.
113. Sonderup MW, Wainwright HC. **Human immunodeficiency virus infection, antiretroviral therapy, and liver pathology.** *Gastroenterol Clin North Am* 2017; **46**:327–343.