

# Prevalence and risk factors of nonalcoholic fatty liver disease in HIV-monoinfection

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**Objective:** To identify the prevalence and risk factors of nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH) and fibrosis in HIV-monoinfected patients.

**Design:** Systematic review and meta-analysis.

**Methods:** We searched Medline and Embase and included studies that enrolled HIV-monoinfected patients with NAFLD defined by imaging and/or liver histology. Data on prevalence and risk factors for NAFLD, NASH and fibrosis were collected for meta-analysis using random effects models.

**Results:** Ten studies were included from the United States of America ( $n=4$ ), Canada ( $n=1$ ), France ( $n=2$ ), Italy ( $n=1$ ), Japan ( $n=1$ ) and China ( $n=1$ ). The prevalence of NAFLD (Imaging studies), NASH and fibrosis (biopsied populations) were 35% [95% confidence interval (CI) 29–42], 42% (95% CI 22–64) and 22% (95% CI 13–34), respectively. Meta-analysis of risk factors showed that high BMI, waist circumference, type 2 diabetes, hypertension, triglycerides and high CD4<sup>+</sup> cell count were associated with NAFLD, whereas HIV viral load, duration of HIV infection, duration of antiretroviral therapy and CD4<sup>+</sup> cell count nadir were not. Patients with high BMI [mean difference (MD) 1.38, 95% CI 0.04–2.71  $P=0.04$ ], fasting glucose (MD 0.80, 95% CI 0.47–1.13  $P<0.00001$ ) and AST level (MD 13.00, 95% CI 4.34–21.65  $P=0.003$ ) were at increased risk of significant liver fibrosis.

**Conclusion:** NAFLD is frequently observed in HIV-monoinfected patients, and NASH is a common cause of unexplained abnormal liver function in patients selected for liver biopsy. Metabolic disorders are key risk factors independently of HIV parameters. Future trials on pharmacological interventions in NASH with fibrosis should include patients with HIV.

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**Keywords:** antiretroviral therapy, fatty liver, fibrosis, HIV, nonalcoholic fatty liver disease, prevalence, risk factors

## Introduction

The prognosis for HIV-infected patients has significantly improved as HAART are now widely used. As a result, AIDS-related mortality has decreased, but non-AIDS comorbidities including chronic liver disease have emerged as diagnostic and management problems [1].

Among these, nonalcoholic fatty liver disease (NAFLD) has become a new concern in the management of patients with HIV.

NAFLD is defined by liver steatosis, the accumulation of triglycerides in the hepatocytes, in the absence of a secondary cause such as excessive alcohol consumption.

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The condition encompasses a spectrum of diseases from nonalcoholic fatty liver to nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis. In non-HIV patients NAFLD is principally the hepatic manifestation of the metabolic syndrome, occurring in the context of insulin resistance, central obesity and dyslipidaemia [2], with disease progression involving a number of complex interacting factors such as genetic susceptibility, oxidative stress and dysbiosis [3]. The prevalence of NAFLD worldwide is estimated to be 25% and is increasing in conjunction with rising levels of obesity, type 2 diabetes mellitus and the metabolic syndrome [4]. Consequently NAFLD is expected to become the leading cause of liver transplantation over the next decade [5].

Identifying patients at risk of NAFLD, especially severe disease with NASH and fibrosis, is critical. In non-HIV patients, prevalence and risk factors of NAFLD and its complications have been well documented, especially in industrialized countries [6].

By contrast, there are more limited data on NAFLD in the HIV-infected population. The pathophysiology might be even more complex due to additional factors including lipodystrophy and HAART [7], and there is still controversy over the prevalence and risk factors associated with the development of NAFLD, NASH and fibrosis, with studies showing both increased [8] and decreased [9] prevalence compared with the general population.

The aim of this study was to perform a systematic review of the medical literature investigating the prevalence and risk factors for NAFLD, NASH and fibrosis in HIV-monoinfected patients.

## Methods

The systematic review was conducted in accordance with guidance from PRISMA [10]. MEDLINE and EMBASE databases were searched on 14 September 2016 for the terms 'HIV,' 'hepatic steatosis' and related synonyms and keywords (Supplementary Table 1, <http://links.lww.com/QAD/B87>). Studies were included comparing adult (aged  $\geq 16$  years) HIV-infected populations with and without NAFLD, as defined by imaging [ultrasound, computed tomography (CT), magnetic resonance spectroscopy (H-MRS) or controlled attenuation parameter (CAP)] or liver histology confirming the presence of hepatic steatosis ( $\geq 5\%$ ) in the absence of viral hepatitis or known excess alcohol consumption. NAFLD with NASH was histologically defined, and significant fibrosis was defined histologically ( $\geq F2$  according to the Metavir, Ishak or NASH Clinical Research Network scores) or by transient elastography at least 7.0 kPa. Studies including patients with chronic hepatitis B or C or alcohol excess

were excluded. Prospective and retrospective observational or interventional studies, randomized controlled trials and systematic reviews were included for review. Non-English abstracts were translated, and the article was requested if the study was possibly relevant. Reference lists of included articles found in the initial database search were also interrogated manually for relevant articles, as well as studies listed as citing included studies on PubMed. Literature reviews, case reports, letters and conference abstracts were excluded.

The results of the search were reviewed by two independent researchers (A.P. and K.P.). Discrepancies in the included studies were resolved by discussion and reviewed by a senior researcher (J.M.) before a final decision on inclusion was made. Data on demographics, diagnostics (prevalence and severity of NAFLD based on imaging and histology) and risk factors for NAFLD was extracted by three independent researchers (A.P., K.P. and J.M.) in duplicate and checked for consistency.

An assessment of included study quality was made using the NIHR Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [11]. Studies could be awarded a maximum 14 points and were reviewed independently by two researchers (J.M. and A.P.). Disagreements were discussed, and a final assessment was made by mutual agreement.

If three or more studies were identified reporting appropriate data on the prevalence or associated risk factors in HIV-infected patients with and without NAFLD, a meta-analysis was performed. Where data were missing or presented in a format that could not be entered into the meta-analysis (e.g. medians with interquartile range), authors were contacted and raw data were requested (for full details of author contact, see Supplementary Table 3, <http://links.lww.com/QAD/B87>).

## Statistical analysis

Individual study prevalences were logit transformed, and a pooled prevalence calculated by an inverse variance weighted random effects model using the restricted maximum likelihood estimator. Pooled prevalences were back-transformed and projected onto forest plots. 95% confidence intervals (CIs) were calculated by the Clopper–Pearson method [12].

Risk factor meta-analysis required studies to present discrete data for dichotomous variables and mean (SD) for continuous variables to allow the calculation of odds ratios (ORs) and MDs, respectively. Data for grades of steatosis were pooled using weighted means to give values for present and absent steatosis. Data were pooled using a random-effects model to generate summary ORs and MDs with 95% CIs. *P* values were calculated for

comparison against the null hypothesis of no effect (OR = 1 or MD = 0). A *P* value less than or equal to 0.05 was considered significant [13].

The *I*<sup>2</sup> statistic and Cochran’s *Q* test were used to quantify statistical heterogeneity between studies in each model. Where heterogeneity was identified, the reasons for this were explored.

Meta-analysis of risk factors was conducted in Review Manager 5.5 [13], and meta-analysis of prevalence data was conducted in R 3.3.0 (Foundation for Statistic Computing, Vienna, Austria) using the meta and metafor packages [14].

## Results

From 410 studies identified in the literature search, 10 studies were included in the review (Fig. 1). The studies were from the United States America (*n* = 4) [8,15–17], Canada (*n* = 1) [18], France (*n* = 2) [19,20], Italy (*n* = 1) [21], Japan (*n* = 1) [22] and China (*n* = 1) [23]. All were single centre, cross-sectional studies (three with case-control). There were no interventional studies. Five studies diagnosed NAFLD with imaging [liver ultrasound (*n* = 2) [15,22], CT (*n* = 1) [21], H-MRS (*n* = 1) [23] or CAP (*n* = 1) [18]], and six studies with liver biopsy [8,16–20] [including a subpopulation in a study primarily using ultrasound scan (USS)] [15] (Table 1).

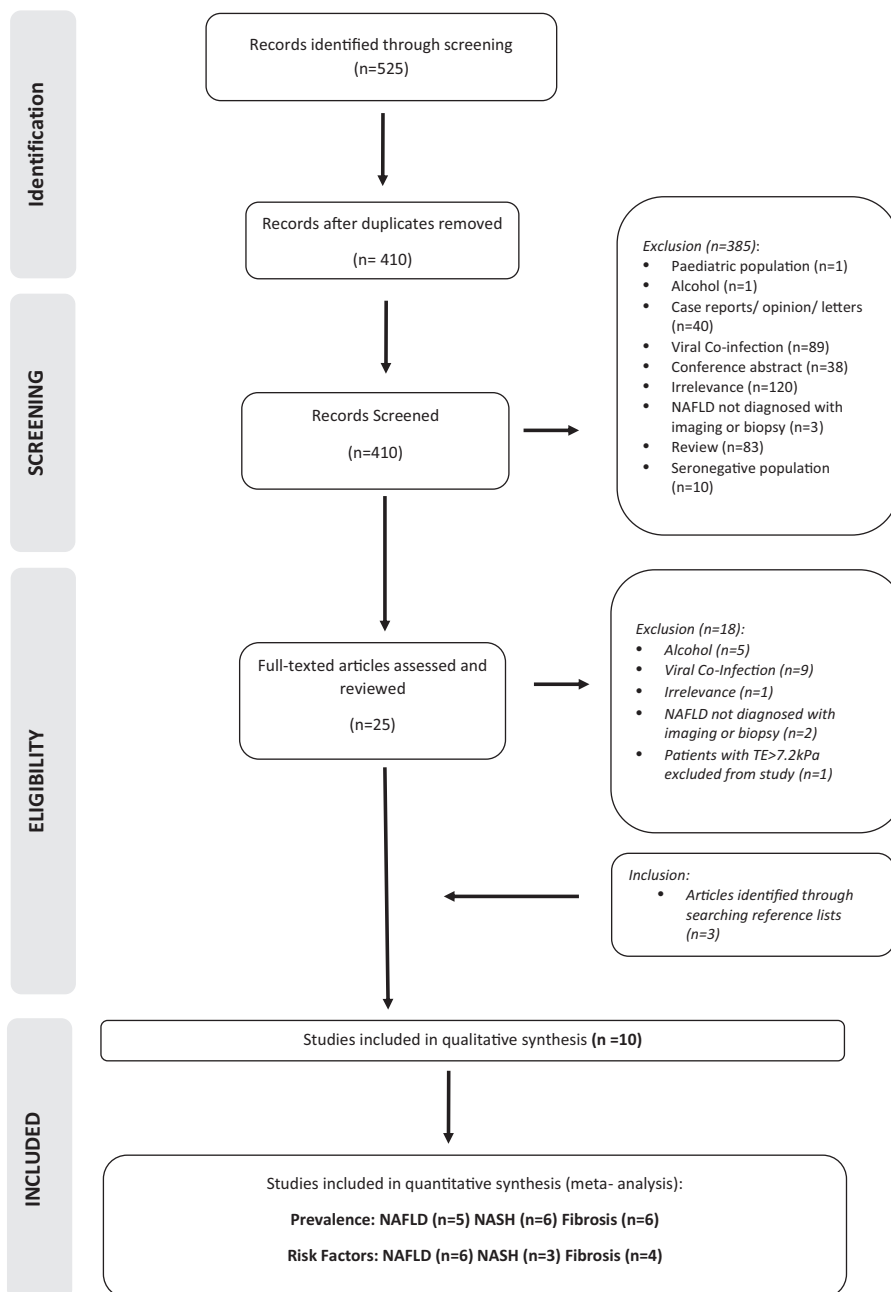


Fig. 1. PRISMA flow diagram for included studies.

Table 1. Summary of included studies.

Author	Year	Country	n	Ethnicity	BMI	Diabetes (%)	Population	Diagnosis of NAFLD	Prevalence of NAFLD, NASH and fibrosis (%)
Crum-Cianflone	2009	USA	216 (Biopsy n = 55)	White 47.7% Black 27.3% Hispanic 13.9% Other 11.1%	26.0 ± 4.1	5.1	Consecutive patients in unspecified military hospital clinic. Biopsy offered with abnormal liver enzymes +/- abnormal USS	USS (liver biopsy in subgroup)	NAFLD: 31.0 NASH: 7.3 ≥ F2 Fibrosis: 3.6
Guaraldi	2008	Italy	225	-	23.8 ± 3.4	13.8	Consecutive patients in metabolic clinic	CT	NAFLD: 36.9 NASH: - ≥ F2 Fibrosis: 20.0
Ingiliz	2009	France	30	-	23.0 ± 3.1	-	ALT or AST > ULN ≥ 2 occasions in previous 6 months	Liver biopsy	NAFLD: 60.0 NASH: 53.3 ≥ F2 Fibrosis: 20.0
Lemoine	2006	France	14	-	23.0 ± 3.4	-	ALT ≥ 2 × ULN over ≥ 3 months. Cases: HIV mono-infection ± insulin resistance. Controls: HIV negative NAFLD and HC	Liver biopsy	NAFLD: 57.1 NASH: 57.1 ≥ F2 Fibrosis: 28.6
Lui	2016	China	80	Chinese Asian 93.8%	23.6 ± 3.9	48.8	Consecutive patients in general ID and HIV metabolic clinic. One participant with excess alcohol (>140 g/week)	H-MRS	NAFLD: 28.8 NASH: - ≥ F2 Fibrosis: 13.8 (TE > 7.0 kPa)
Morse	2015	USA	62	White 64.5% Black 8.1% Asian 3.2% Other 24.2% Hispanic 29.0% East Asian 97.5%	28.0 ± 4.4	9.7	AST or ALT > ULN ≥ 3 occasions over ≥ 6 months	Liver biopsy	NAFLD: 72.6 NASH: 54.8 ≥ F2 Fibrosis: 19.4
Nishijima	2014	Japan	435	-	22.8 ± 3.8	5.1	All HIV patients with available USS data	USS	NAFLD: 31.0 NASH: - ≥ F2 Fibrosis: 28.6
Sterling	2014	USA	14	White 57.0%	29.9 ± 7.4	0.0	AST or ALT 1.25–5 × ULN over ≥ 6 months. People with diabetes excluded	Liver biopsy	NAFLD: 64.3 NASH: 28.6 ≥ F2 Fibrosis: 35.7
Vodkin	2015	USA	33	Hispanic 51.5%	29.8 ± 6.0	18.2	Cases: liver biopsies of NAFLD in HIV mono-infection. Controls: age and sex-matched cases of HIV negative NAFLD	Liver biopsy	NAFLD: N/A NASH: 63.6 ≥ F2 Fibrosis: 33.3
Vuille-Lessard	2016	Canada	300	White 42.0% Black 40.0% Hispanic 13.7% South Asian 3.3%	26.0 ± 4.3	11.3	Consecutive and unselected HIV mono-infected patients with TE and CAP	CAP	NAFLD: 48.0 NASH: - ≥ F2 Fibrosis: 15.0 (LS ≥ 7.1 kPa)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI expressed as mean ± SD; CAP, controlled attenuation parameter; CT, computed tomography; HC, healthy controls; H-MRS, proton-magnetic resonance spectroscopy; ID, infectious diseases; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; TE, transient elastography; ULN, upper limit of normal; USS, ultrasound scan.

Seven authors provided additional data, so it could be incorporated into the meta-analysis [15,17–20,22,23] (Supplementary Table 2, <http://links.lww.com/QAD/B87>).

### Demographics

The study populations were almost exclusively male (>90% in all studies except one) [18]. In keeping with the geographical location of the studies, there was variation in population ethnicity. The two studies from the Far East had more than 90% East Asian participants, whereas studies in Europe and America included more heterogeneous populations. The proportion of black and Hispanic participants ranged between 8.1–40.0% and 13.7–51.5%, respectively (Table 1).

The mean BMI ranged from 22.8 (imaging study, Japan) [22] to 29.9 kg/m<sup>2</sup> (biopsy study, the United States of America) [16]. Five studies had a mean BMI less than 25 kg/m<sup>2</sup>. The prevalence of type 2 diabetes ranged from 0% (diabetes was an exclusion criteria) [16] to 48.8% (recruiting from a metabolic clinic) [23] (Table 1).

Six studies investigated and excluded other causes of chronic liver disease [16–21]. One study documented but did not exclude drugs known to cause secondary steatosis [15], and one study explicitly documented exclusion of patients on methotrexate, tamoxifen, amiodarone and steroids [8].

### Study quality

Studies were of moderate-to-poor quality, with scores ranging from 5 to 8 (maximum score 14) according to the NIH Quality Assessment Tool (Supplementary Table 3, <http://links.lww.com/QAD/B87>). Studies were primarily limited by retrospective, cross-sectional design with no longitudinal follow-up.

### Nonalcoholic fatty liver disease prevalence

To reduce heterogeneity and improve the accuracy of the result, NAFLD prevalence analysis was restricted to studies based on imaging. Five studies including 1256 patients were analysed [15,18,21–23]. Pooled prevalence of NAFLD prevalence was 35.3% (95% CI 28.8–42.5) (Fig. 2). There was significant heterogeneity between individual studies ( $I^2 = 85.3\%$   $P < 0.001$ ).

### Nonalcoholic steatohepatitis prevalence

Six studies including 208 cases with histological confirmation of NASH were analysed [8,15–17,19,20]. The pooled prevalence of NASH was 41.7% (95% CI 22.3–64.0). There was significant heterogeneity between individual studies ( $I^2 = 83.1\%$   $P < 0.0001$ ) (Fig. 2), which may be a consequence of variation in patient selection for liver biopsy (Table 1). Liver histology findings are summarized in Supplementary Table 4, <http://links.lww.com/QAD/B87>.

### Fibrosis prevalence

Six studies with 208 cases with data on significant fibrosis, defined by at least F2 fibrosis on liver histology, were included [8,15–17,19,20]. Pooled prevalence of significant fibrosis was 21.7% (95% CI 13.1–33.7) (Fig. 2). The results were more consistent across studies, but significant heterogeneity remained ( $I^2 = 59.3\%$   $P = 0.031$ ).

In addition, two studies included data on the noninvasive assessment of significant liver fibrosis in nonbiopsied populations, but there were insufficient data for meta-analysis. Liu *et al.* reported that in patients with NAFLD and HIV, one of 23 (4.3%) had FIB-4 score 2.67 or more and six of 23 (27.3%) had significant fibrosis defined by increased liver stiffness on transient elastography ( $\geq 7.0$  kPa). Vuille-Lessard *et al.* did not separate patients with and without NAFLD for their fibrosis assessment but reported FIB-4 score 2.67 or more in 20 of 300 (6.7%) and increased liver stiffness ( $\geq 7.1$  kPa) in 45 of 300 (15%) in the whole cohort of HIV-monoinfected patients [18,23].

### Risk factors for nonalcoholic fatty liver disease

Six studies provided data on the risk factors for NAFLD in HIV-monoinfected patients with sufficient data to perform meta-analysis on 17 variables [15,16,18,21–23].

BMI (MD 2.92 95% CI 2.14–3.70,  $P < 0.00001$ ), waist circumference [MD 8.05 (5.46–10.64)  $P < 0.00001$ ], type 2 diabetes [OR 1.61 (1.09–2.39)  $P = 0.02$ ], hypertension [OR 1.75 (1.27–2.41)  $P = 0.0006$ ], high triglycerides [MD 61.52 (24.31–98.74)  $P = 0.001$ ], high total cholesterol [MD 6.19 (0.93–11.45)  $P = 0.02$ ], low HDL cholesterol [MD -4.21 (-6.82 to -1.59)  $P = 0.002$ ], high LDL cholesterol [MD 5.80 (2.01–9.58)  $P = 0.003$ ], high fasting glucose [MD 0.43 (0.18–0.68)  $P = 0.0007$ ], high alanine aminotransferase [MD 15.98 (8.04–23.92)  $P < 0.0001$ ], high aspartate aminotransferase (AST) [MD 5.27 (2.66–7.88)  $P < 0.0001$ ] and high CD4<sup>+</sup> T-cell count [MD 54.83 (11.55–98.11)  $P = 0.0$ ] were associated with NAFLD. Age, suppressed HIV viral load, duration of HIV infection, duration of HAART and CD4<sup>+</sup> nadir were not associated with NAFLD (Fig. 3). There were insufficient data to meta-analyse the diagnosis of dyslipidaemia (based on the use of lipid-lowering drugs).

There was significant statistical heterogeneity between studies for BMI ( $I^2 = 56\%$   $P = 0.04$ ), triglycerides ( $I^2 = 73\%$ ,  $P = 0.001$ ) and HDL ( $I^2 = 55\%$ ,  $P = 0.05$ ).

Sensitivity analysis with data restricted to imaging studies alone, and with Crum-Cianflone USS data replaced with their biopsy data, did not change any of the outcomes relationship with NAFLD (data not shown).

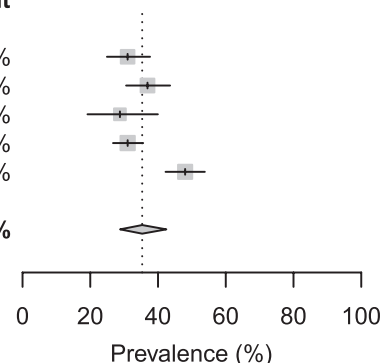
### Risk factors for nonalcoholic steatohepatitis and fibrosis

Three studies provided data for meta-analysis on patients with a histological diagnosis of NASH [15,17,19]. None

(a) **NAFLD Prevalence**

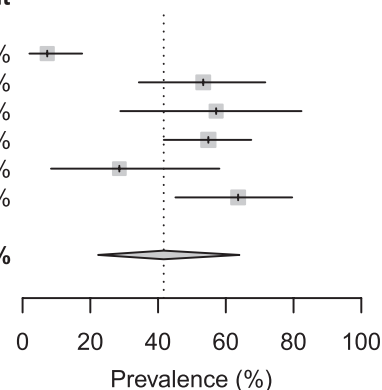
Study	Events	Total	Prevalence (%)	95% CI	Weight
Crum-Cianflone	67	216	31.02	[24.92; 37.65]	20.2%
Guaraldi	83	225	36.89	[30.57; 43.56]	20.7%
Lui	23	80	28.75	[19.18; 39.95]	15.1%
Nishijima	135	435	31.03	[26.71; 35.62]	22.3%
Vuille-Lessard	144	300	48.00	[42.22; 53.82]	21.8%
<b>Random effects model</b>		<b>1256</b>	<b>35.32</b>	<b>[28.80; 42.45]</b>	<b>100%</b>

*Heterogeneity: I<sup>2</sup>=85.3%, tau<sup>2</sup>=0.0947, P<0.0001*

(b) **NASH Prevalence**

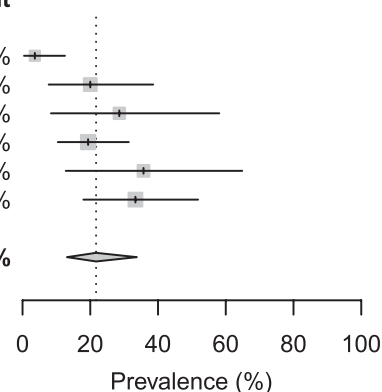
Study	Events	Total	Prevalence (%)	95% CI	Weight
Crum-Cianflone	4	55	7.27	[ 2.02; 17.59]	15.8%
Ingiliz	16	30	53.33	[34.33; 71.66]	17.5%
Lemoine	8	14	57.14	[28.86; 82.34]	15.6%
Morse	34	62	54.84	[41.68; 67.52]	18.6%
Sterling	4	14	28.57	[ 8.39; 58.10]	14.9%
Vodkin	21	33	63.64	[45.12; 79.60]	17.6%
<b>Random effects model</b>		<b>208</b>	<b>41.67</b>	<b>[22.30; 64.00]</b>	<b>100%</b>

*Heterogeneity: I<sup>2</sup>=83.1%, tau<sup>2</sup>=1.1, P<0.0001*

(c) **Fibrosis Prevalence**

Study	Events	Total	Prevalence (%)	95% CI	Weight
Crum-Cianflone	2	55	3.64	[ 0.44; 12.53]	11.2%
Ingiliz	6	30	20.00	[ 7.71; 38.57]	17.7%
Lemoine	4	14	28.57	[ 8.39; 58.10]	14.0%
Morse	12	62	19.35	[10.42; 31.37]	21.9%
Sterling	5	14	35.71	[12.76; 64.86]	14.9%
Vodkin	11	33	33.33	[17.96; 51.83]	20.4%
<b>Random effects model</b>		<b>208</b>	<b>21.72</b>	<b>[13.13; 33.74]</b>	<b>100%</b>

*Heterogeneity: I<sup>2</sup>=59.3%, tau<sup>2</sup>=0.3358, P=0.0311*



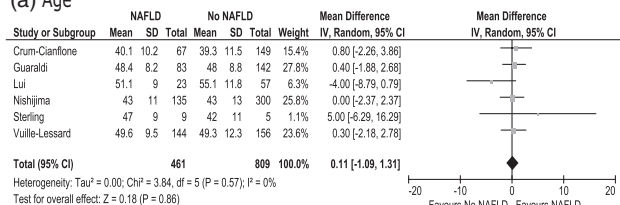
**Fig. 2. Forest plots for disease prevalence.** (a) Nonalcoholic fatty liver disease, diagnosed by imaging; (b) nonalcoholic steatohepatitis, diagnosed by liver biopsy; (c) significant fibrosis, defined as at least F2 fibrosis diagnosed by liver biopsy.

of the reported parameters were associated with NASH, although the studies were small in size (141 cases) with data available on only limited variables (Supplementary Fig. 1, <http://links.lww.com/QAD/B88>).

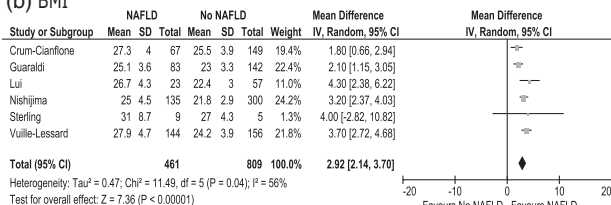
Four studies provided data on 11 risk factors for significant fibrosis (defined as  $\geq$ F2 fibrosis on liver biopsy or  $\geq$ 7.1 kPa by transient elastography) including 379 cases. Data were not included from Liu *et al.* as factors associated with fibrosis were assessed in a population with HIV-positive and HIV-negative cases. Three studies were based on liver histology [15,17,19], but the results were

heavily weighted by one study defining significant fibrosis by transient elastography (liver stiffness  $\geq$ 7.1 kPa,  $n=300$ ) [18]. BMI (MD 1.38 95% CI 0.04–2.71  $P=0.04$ ), fasting glucose [MD 0.80 (0.47–1.13)  $P<0.00001$ ] and AST level [MD 13.00 (4.34–21.65)  $P=0.003$ ] were associated with fibrosis, whereas male sex [OR 0.27 (0.15–0.51)  $P<0.0001$ ] and black ethnicity [OR 0.18 (0.08–0.44)  $P=0.0002$ ] were protective factors. CD4<sup>+</sup> cell count (NASH) and duration of HIV infection (fibrosis) were the only HIV-specific variables with data for meta-analysis, neither of which were associated with the outcome of interest (Fig. 4).

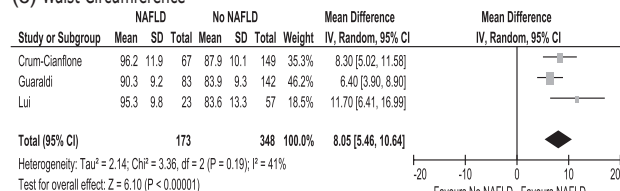
(a) Age



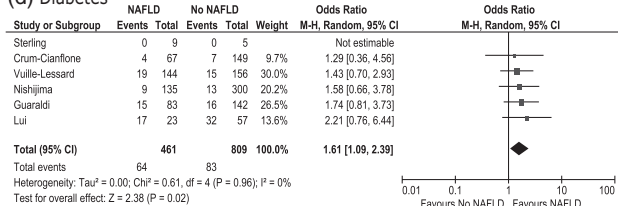
(b) BMI



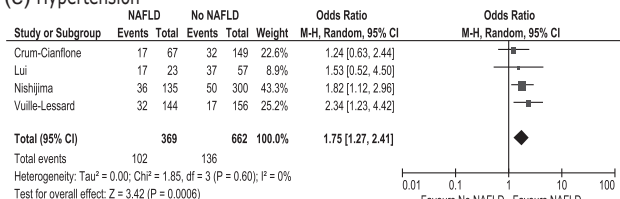
(c) Waist Circumference



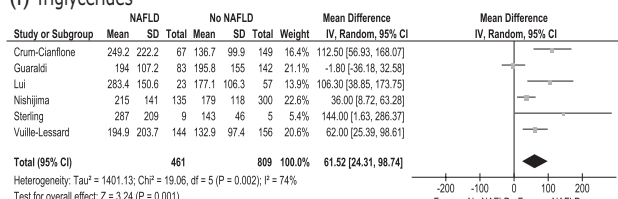
(d) Diabetes



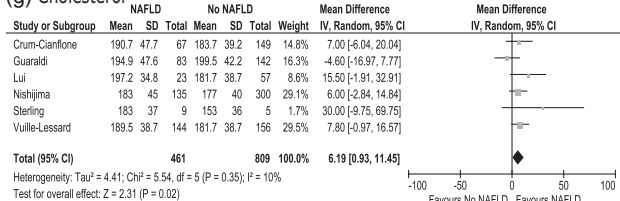
(e) Hypertension



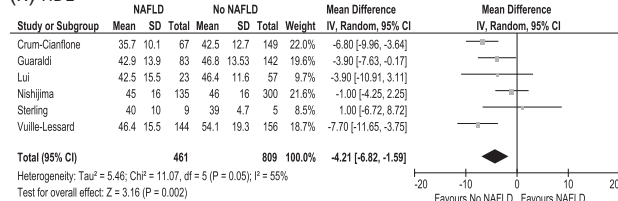
(f) Triglycerides



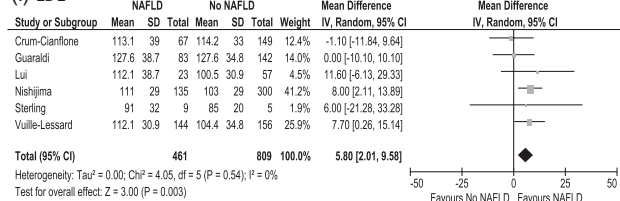
(g) Cholesterol



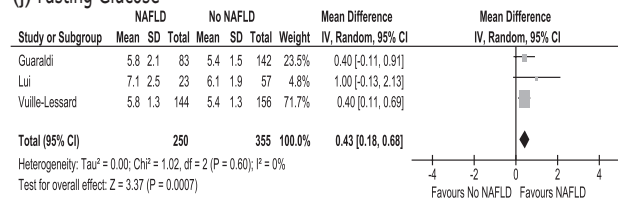
(h) HDL



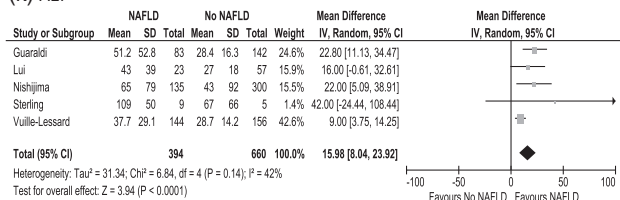
(i) LDL



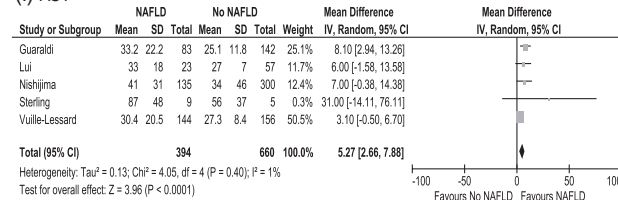
(j) Fasting Glucose



(k) ALT

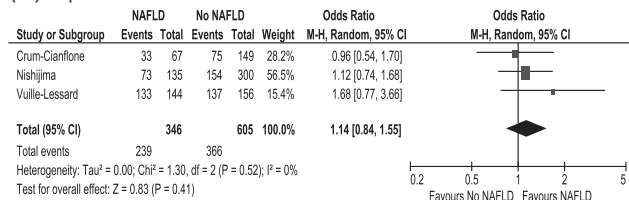


(l) AST

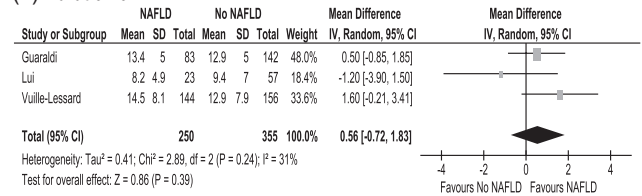


**Fig. 3. Forest plots for nonalcoholic fatty liver disease risk factors.** (a) Age, (b) BMI, (c) waist circumference, (d) diabetes, (e) hypertension, (f) triglycerides, (g) total cholesterol, (h) HDL, (i) LDL, (j) fasting glucose, (k) ALT, (l) AST, (m) suppressed viral load, (n) duration of HIV infection, (o) CD4<sup>+</sup> cell count, (p) CD4<sup>+</sup> nadir, (q) duration of HAART. The diagnosis of diabetes and hypertension were based on the concomitant use of medications for these conditions. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

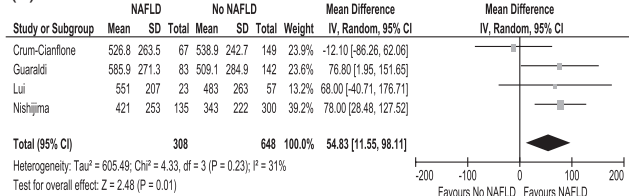
(m) Suppressed Viral Load



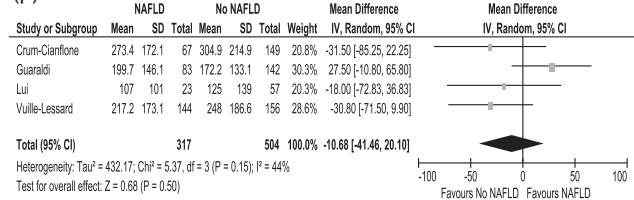
(n) Duration of HIV



(o) CD4 Count



(p) CD4 Nadir



(q) Duration of HAART

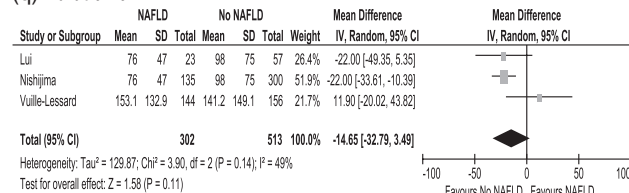


Fig. 3. (Continued)

There was significant statistical heterogeneity for age ( $I^2 = 85\%$   $P = 0.0002$ ).

Discussion

The current study provides the first systematic review of the literature with meta-analysis examining the prevalence and risk factors of NAFLD, NASH and fibrosis in HIV-monoinfected patients.

Ten studies met criteria for inclusion in the review. We carefully excluded studies that were confounded with HCV infection or high alcohol intake, for example [9,24], and the small number of studies enrolled in our review highlights that NAFLD in HIV-monoinfection has been a long-neglected field of research.

Based on radiological criteria, our review found a prevalence of NAFLD in HIV-monoinfected of 35%. Prevalence estimates in the general population vary significantly with diagnostic modality and study population. A recent systematic review has reported a worldwide prevalence of NAFLD diagnosed by imaging at 25%. Stratified by region, the prevalence in Asia, Europe and the United States America was 27, 24 and 24%, respectively [4]. However, the figure increases up to 70% in diabetic patients and over 90% among obese patients [25].

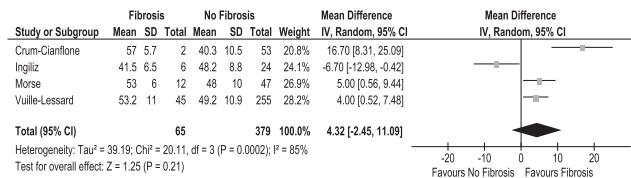
Only one study has directly compared the prevalence of liver steatosis between HIV and non-HIV patients [9]. The study showed a lower prevalence in HIV patients at 13 vs. 19% ( $P = 0.02$ ) in non-HIV patients, but the study included 9% of patients with positive HCV antibodies that may have influenced these results (genotype 3 is a recognized cause of steatosis).

In contrast to this, our data suggest that the prevalence of NAFLD in HIV-monoinfected patients may be higher (35%) than the general population (25%). Our meta-analysis confirms that parameters of the metabolic syndrome are significantly associated with the development of NAFLD in HIV as observed in the general population. Significantly, higher CD4+ cell count was also associated with NAFLD, whereas duration of HIV infection or HAART, HIV viral load and CD4+ cell count nadir were not. This suggests that well treated HIV patients might be at higher risk of NAFLD, although interestingly age and HAART exposure were not associated.

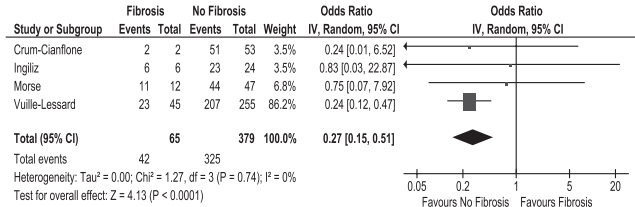
There were insufficient data to meta-analyse exposure by drug class. Only the study by Guaraldi *et al.* [21] identified cumulative nucleoside reverse transcriptase inhibitors exposure to be associated with NAFLD. This was in a population with a median exposure of 124 months, and given the time period this may have included hepatotoxic 'D-drugs' (didanosine, zalcitabine and stavudine), although this is not specified in the article. Four other



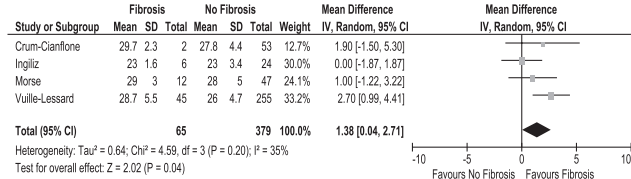
(a) Age



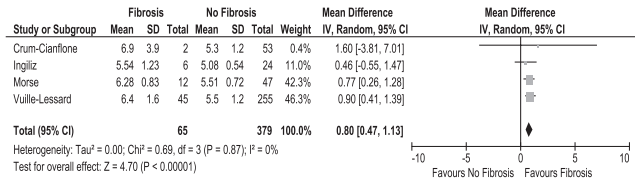
(b) Male Gender



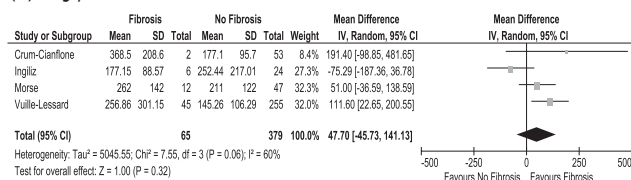
(c) BMI



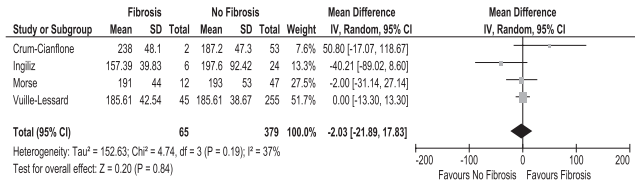
(d) Fasting Glucose



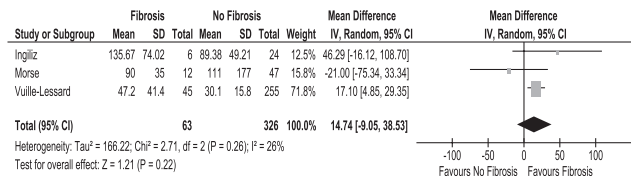
(e) Triglycerides



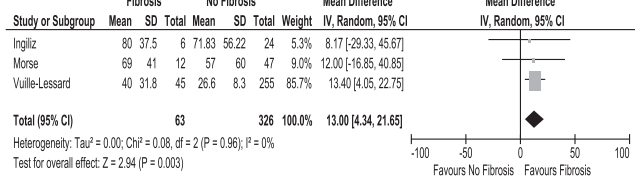
(f) Cholesterol



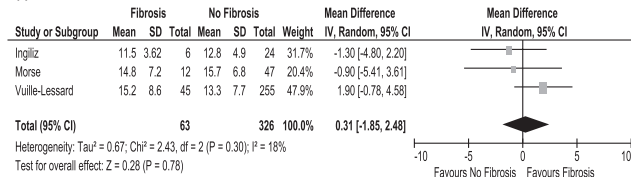
(g) ALT



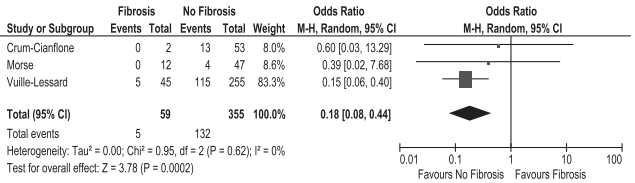
(h) AST



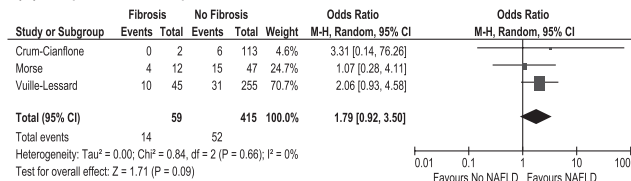
(i) Duration of HIV



(j) Black Ethnicity



(k) Hispanic Ethnicity



**Fig. 4. Forest plots for fibrosis risk factors.** (a) Age, (b) male sex, (c) BMI, (d) fasting glucose, (e) triglycerides, (f) total cholesterol, (g) ALT, (h) AST, (i) duration of HIV infection, (j) black ethnicity, (k) Hispanic ethnicity. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

studies in the review examined drug class exposure and found no association with NAFLD [15,18,22,23].

Establishing the exact prevalence of NAFLD is difficult due to heterogenous data [4]. This is partly explained by

inconsistent diagnostic methods; studies included in our review used USS, CT, H-MRS and CAP, all with differing sensitivities for detecting steatosis, making comparisons difficult [26]. Studies also vary in population selection. For instance, participants in two studies in this

review were drawn from specialist metabolic clinics where there were inevitably higher rates of diabetes. By contrast, other studies were drawn from less-selected general infectious disease clinics, for example [18].

Assessing the severity of NAFLD is crucial. The presence of fibrosis is the strongest predictor of liver-related morbidity in non-HIV patients with NAFLD [27], and patients with NASH are more at risk of liver fibrosis progression. The diagnosis of NASH still relies on liver histology, an invasive procedure which is more infrequently performed with the development of noninvasive markers of liver disease. Therefore, histological data are scarce, and our review included only six studies using liver biopsies. The prevalence of NASH in patients selected for liver biopsy was 42%, and significant fibrosis 22%. Clearly, this is an enriched population through the selection bias of an invasive test, and unsurprisingly noninvasive tests such as FIB-4 estimate a much lower prevalence of 4 and 6% in nonbiopsied populations, although the same two studies estimated 27 and 15% had significant fibrosis by transient elastography.

It is debated how this compares with the general population; Vodkin *et al.* [8] showed a higher rate of NASH in HIV patients (64 vs. 36%), whereas a recent systematic review reported similar results in biopsied cohorts (59%) [4]. The significant statistical heterogeneity between studies reflects the small and varied study populations, which makes an accurate study of the prevalence of severe disease difficult. This is exacerbated in the assessment of NASH by the evolution of histological definitions of the disease over the last 10 years, and one included study used a definition of NASH now not widely used, which may partly explain the unusually low prevalence (7%) in that study [15].

We found that increased BMI and fasting glucose were significantly associated with fibrosis, implying that metabolic disorders and in particular obesity-related adipose tissue dysfunction might play a key role in the development of liver fibrosis.

Taken together, these results warrant three comments. First, imaging studies suggest that NAFLD is common in HIV-monoinfected patients but limited histological data without long-term follow-up on the incidence of NASH/fibrosis in the post-HAART era mean we still do not know what the rate is of fibrosis progression as compared with HIV-negative patients with NAFLD. It is possible that although metabolic factors predominate in disease pathogenesis, HIV infection and/or drug exposure could potentiate the effects in the liver such that disease progresses with milder features of the metabolic syndrome, which may explain why some studies show NAFLD occurring in HIV-infected patients with lower BMI [28]. However, to address this question

longitudinal studies with good-quality histological data are needed.

Second, patients with HIV infection and features of the metabolic syndrome require a full diagnostic workup for NAFLD. The prevalence of NAFLD is rising rapidly in the Western world in parallel with increasing obesity and the metabolic syndrome and has become a prominent cause of liver-related morbidity and requirement for liver transplantation [29]. Both NAFLD and HIV also confer increased risk of cardiovascular disease [30]. Therefore, the management of dyslipidaemia, hypertension, diabetes mellitus and obesity in a multi-disciplinary setting is therefore an essential aspect of HIV care and is already an integral service offered to patients in many centres. This needs to be combined with effective liver assessment and risk stratification with noninvasive tools such as transient elastography and/or biochemical markers (e.g. Enhanced Liver Fibrosis score and NAFLD fibrosis score) [31], to identify patients who need more dedicated input from a specialist hepatologist. However, the performance of these tools has been poorly validated in HIV monoinfected patients, and the disparity between estimates of fibrosis in the studies reporting both FIB-4 and transient elastography data highlights this point.

Third, we are entering a new era in the management of NAFLD. The mainstay of treating the disease has long been based on life style modification including weight loss and physical activity [32]. However, only a small proportion of patients successfully achieve this. Significantly, multiple new treatments are emerging for advanced disease [33]. Yet HIV infection is invariably an exclusion factor for patients enrolled in these trials. The data from this review show how therapeutic options are at least as important in patients with HIV, and it is essential such trials do not exclude HIV patients.

Our study has three main limitations: first, the small number of studies enrolled limits the interpretation of our findings. Only 10 articles were included in the review, mainly of moderate-to-low quality, and most of these studies enrolled a limited number of patients. There was variable reporting of relevant data, which reduced the number of analyses we could perform, and there were no data on disease incidence and the factors associated with this. Second, we were unable to meta-analyse data on drug class exposure, and there is no data on the impact of more modern treatment options such as integrase inhibitors. Third, our analysis on risk factors of fibrosis was heavily weighted towards a large Canadian study based on noninvasive markers [18]. Clearly, our systematic review highlights the lack of homogeneity in the assessment of NAFLD in HIV, and the urgent need for additional high-quality data from a larger number of HIV-monoinfected patients with NAFLD.

## Conclusion

NAFLD is common in HIV-monoinfected patients. Metabolic disorders are key risk factors of NAFLD independent of HIV parameters and predict its complications. The strong association between obesity and liver fibrosis in HIV-monoinfected patients supports the adipocentric concept of liver fibrogenesis in this population. This needs to be confirmed by additional studies. Our systematic review underlines the need for additional data on NAFLD in HIV infection as well as a better standardized assessment and management of the disease.

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## Conflicts of interest

M.L. has served as a consultant on HIV NAFLD for MSD and GSK Healthcare and received fees from them. J.M., A.P., A.S., K.P., M.N. and M.T. have nothing to declare.

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