Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in patients with HIV

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Liver disease is a leading cause of morbidity and mortality among people with HIV, and in this era of safer and more effective hepatitis C therapy, non-alcoholic fatty liver disease (NAFLD) could soon emerge as the most common liver disease in this population. NAFLD is common among patients with HIV, and might be more likely to progress to non-alcoholic steatohepatitis (NASH) and NAFLD-related fibrosis or cirrhosis in these patients than in individuals without HIV. Several mechanisms of NAFLD pathogenesis are postulated to explain the disease severity in patients with HIV; these mechanisms include the influence of the gut microbiome, and also metabolic, genetic, and immunological factors. Although treatment strategies are currently based on modification of NAFLD risk factors, many new drugs are now in clinical trials, including trials specifically in patients with HIV. Thus, the identification and risk-stratification of patients with HIV and NAFLD are becoming increasingly important for accurately counselling of these patients regarding their prognosis and for establishing the most appropriate disease-altering therapy.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease in the USA[1] and might affect more than 25% of the population worldwide.[2] NAFLD represents a spectrum of conditions that include the hepatic accumulation of fatty acids (steatosis), the development of an inflammatory response that causes hepatocellular injury (known as non-alcoholic steatohepatitis [NASH]), and NAFLD-associated fibrosis and cirrhosis. Although the prevalence of NAFLD varies widely depending on the population sampled and the assessment technique used, NAFLD is estimated to account for 50–75% of chronic liver disease in the USA,[3] and is expected to soon be the leading cause of cirrhosis and hepatocellular carcinoma.

HIV is a global health issue, and approximately 35 million people in the world are infected with the virus.[4] As antiretroviral therapy (ART) has become increasingly effective and HIV has evolved into a chronic disease, non-AIDS-related causes of morbidity and mortality have become increasingly important. Liver disease is now the second leading cause of non-AIDS-related death among people with HIV.[5] Although the high prevalence of steatosis and steatohepatitis has been recognised in patients with HIV since the 1980s,[6–9] the previously uncertain effect of these syndromes on patient outcomes, difficulty with non-invasive diagnosis, and few therapeutic options have led to the under-recognition and under-treatment of NAFLD in these patients. However, as the prevalence of metabolic syndrome and NAFLD rise and a multitude of novel therapeutic agents are entering clinical trials for NAFLD (both in the general population and in patients with HIV), a more concerted effort to diagnose, stage, and treat these patients will be essential to combating the NAFLD epidemic.

This Review focuses on the literature regarding the epidemiology and pathogenesis of NAFLD in patients with HIV, and highlights current and future approaches to the diagnosis and treatment of this population.

Epidemiology of NAFLD in HIV: prevalence, risk factors, and severity

Liver disease is a leading cause of morbidity and mortality among patients with HIV. It accounted for 13% of deaths in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) multicentre cohort between 1999–2011, making liver disease the second leading non-AIDS-related cause of death in this cohort.[5] Although the burden of liver disease among patients with HIV has mostly been attributed to hepatitis C virus (HCV), HCV treatments are now safe and effective in patients with HIV–HCV co-infection and so the clinical impact of HCV is likely to decline in the coming decades. Conversely, the morbidity and mortality due to NAFLD in this population, as in the general population, is expected to continue to rise.[10]

Prevalence

The prevalence of NAFLD in patients with HIV is poorly characterised and has varied considerably over time, which in many ways reflects the various eras of HIV treatment. In the pre-ART era, NAFLD might have been present in up to 85% of patients with HIV,[6–9] and it was thought, at the time, to be caused by malnutrition and opportunistic infections. In the early ART era, up to 60% of patients with HIV had NAFLD,[11] and additional studies reported severe drug-induced liver injury and microvesicular steatosis. Mitochondrial injury due to the use of dideoxynucleoside analogues, such as didanosine and stavudine, was often implicated in these severe cases;[12–18] thus, these agents are no longer recommended and are rarely used in the USA.

In the modern ART era, despite a shift away from the most hepatotoxic agents, NAFLD remains highly prevalent in patients with HIV, and estimates range from 13% to 55% depending on the population sampled and the assays used to diagnose NAFLD (table).[11,19–30] Unfortunately, almost all of the large studies rely on non-invasive imaging-based techniques to diagnose

	Patient population	Number of patients with HIV mono-infection	NAFLD diagnostic assay	NAFLD prevalence in patients with HIV mono-infection	Predictors of NAFLD in patients with HIV mono-infection
Hadigan et al (2007)[19]	Consecutive patients with HIV who did not abuse alcohol	33	MRS	42·0%	High HOMA-IR, visceral adiposity, high BMI, and high plasma ALT and triglyceride concentrations
Guaraldi et al (2008)[20]	Patients with HIV who did not abuse alcohol or have viral hepatitis	225	Liver-to-spleen attenuation on CT	36·9%	Male sex and large waist circumference
Ingiliz et al (2009)[21]	Patients with chronic elevation in liver test results that had no genetic cause and had no HCV, HBV, or autoimmune disease	30	Liver biopsy	Of the total patient cohort, 60·0% had steatosis and 53·0% had NASH	High fasting plasma glucose concentration
Crum-Cianflone et al (2009)[10]	Patients with HIV who did not have HCV or HBV	267	Ultrasound and 55 liver biopsies	31·0% of patients assessed by ultrasound had NAFLD; 36·0% of patients assessed by biopsy had NAFLD and 20·0% had NASH	Large waist circumference, and high plasma triglyceride and LDL concentrations
Li Vecchi et al (2012)[22]	Patients with HIV mono-infection or HIV–HCV co-infection	57	Ultrasound and transient elastography	54·0%	Lipodystrophy, high plasma triglyceride concentration, metabolic syndrome, high plasma cholesterol concentration, and ART use for more than 1 year
Li Vecchi et al (2013)[23]	Patients with HIV mono-infection or HIV–HCV co-infection	69	Ultrasound and transient elastography	46·3%	High plasma triglyceride concentrations and diabetes
Sterling et al (2013)[24]	Patients with HIV who did not have HCV or HBV, did not abuse alcohol, and did not have diabetes mellitus or elevated liver test results	14	Liver biopsy	Of the total patient cohort, 65·0% had steatosis and 26·0% had NASH	High HOMA-IR and serum GGT concentrations, which predict steatosis
Nishijima et al (2014)[25]	Patients with HIV who did not have HBV or HCV, and did not abuse alcohol	435	Ultrasound	31·0%	High BMI and dyslipidaemia
Price et al (2014)[26]	Multicenter AIDS Cohort Study: patients with HIV who did not abuse alcohol	465	Liver-to-spleen attenuation on CT	13·0%	*PNPLA3* genotype and cumulative dideoxynucleoside exposure
Macias et al (2014)[27]	Patients with HIV in a walk-in clinic	505	Transient elastography with CAP	40·0%	High BMI, and high fasting plasma glucose and plasma triglyceride concentrations
Sulyok et al (2015)[28]	Outpatients with HIV mono-infection or HIV–HCV co-infection	136	Transient elastography with CAP	49·5%	High BMI, diabetes, and hypertension
Morse et al (2015)[29]	Patients with HIV who had elevated serum ALT concentrations for 6 months, were on ART, and did not have chronic liver disease	62	Liver biopsy	Of the total patient cohort, 55·0% had NASH and 18·0% had bridging fibrosis	Diabetes, obesity, and *PNPLA3* genotype
Lui et al (2016)[30]	Patients with HIV who did not have HBV or HCV	80	Transient elastography and MRS	28·7%	High BMI, metabolic syndrome, high fasting glucose and serum triglyceride concentrations

NAFLD=non-alcoholic fatty liver disease. MRS=magnetic resonance spectroscopy. HOMA-IR=homeostasis model assessment of insulin resistance. BMI=body-mass index. ALT=alanine aminotransferase. NASH=non-alcoholic steatohepatitis. HCV=hepatitis C virus. HBV=hepatitis B virus. ART=antiretroviral therapy. GGT=γ-glutamyl transferase. CAP=controlled attenuation parameter.

Table: **Prevalence of non-alcoholic fatty liver disease in patients with HIV mono-infection in the modern ART era**

NAFLD, and very little literature incorporates histological assessment of NASH, fibrosis, or both. Additionally, the characteristics of the surveyed populations vary considerably, which affects prevalence estimates. Although the data are somewhat conflicting, studies have shown that many risk factors for NAFLD in the general population—including measures of obesity, insulin resistance, and hypertriglyceridaemia, which are components of metabolic syndrome—are also risk factors in patients with HIV. Viral factors, including HIV viral load and specific ART characteristics, have not been consistently identified as independent predictors of NAFLD in the modern ART era.[11,25] However, patients with HIV and NAFLD had a lower body-mass index (BMI) and higher baseline levels of physical activity[31] than did patients with NAFLD only, which suggests that additional pathogenic factors are present in patients with HIV.[31]

The prevalence of NAFLD might be even higher in patients with HIV–HCV co-infection, with reports ranging from 23% to 72%.[32–41] Patients with HIV–HCV co-infection have been better studied than those with HIV mono-infection owing to the more frequent use of liver biopsy in patients with co-infection. Among these patients, the strongest risk factors for the presence of steatosis are components of metabolic syndrome (which, as mentioned above, are risk factors for NAFLD) and also HCV genotype 3. Steatosis is likely to be more common among patients with HIV–HCV co-infection than among patients with HCV mono-infection,[40] suggesting an important effect of HIV in the pathogenesis of steatosis. Additionally, the presence of steatosis might be more

strongly associated with more advanced fibrosis among patients with HIV–HCV co-infection than among patients with HCV mono-infection,[40] perhaps suggesting a synergistic effect of NAFLD and HCV on hepatic fibrogenesis in patients with co-infection.

Of particular importance, NAFLD is by far the most likely cause of chronic hepatitis in patients with HIV who test negative for chronic viral hepatitis.[21,29,42] In one study, 62 patients with chronic elevation in alanine aminotranferase concentrations who did not have viral hepatitis or any other known chronic liver disease, and who were on ART for over a year, underwent liver biopsy, and most patients were found to have NAFLD (73%); additionally, many of the patients in the total cohort had NASH (55%), bridging fibrosis (18%), or both.[29] Insulin resistance, obesity, and polymorphisms of the *PNPLA3* gene were significantly associated with the risk of NASH and fibrosis in this cohort, although the baseline characteristics of patients with NAFLD and those with non-specific findings considerably overlapped, highlighting the need for the use of liver biopsy samples to diagnose NAFLD in many cases. Similar findings were reported in a smaller series of 30 patients who underwent liver biopsy after 6 months of showing elevation in a panel of liver test results (including aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase, and serum γ-glutamyl transferase) in the absence of viral hepatitis, autoimmune disease, and metabolic liver diseases: of the total patient cohort, 60% had steatosis, 53% had NASH, and 20% had bridging fibrosis or cirrhosis.[21]

Disease progression

The prevalence and incidence of NASH and fibrosis are difficult to precisely estimate because of the ongoing reliance of these diagnoses on liver histology. In the general population, only a minority of patients with steatosis will develop NASH, although a study[43] of a series of paired biopsy samples reported the rates of NASH progression to be more than 30%. Among patients with NASH, up to a third will develop progressive fibrosis.[44] A meta-analysis has estimated that the progression of fibrosis occurs at an average rate of one stage every 14 years for patients with steatosis who have no fibrosis at baseline, compared with one stage every 7 years for patients with NASH.[43] However, the natural history of fibrosis is quite variable even among these groups.

Data on disease progression in patients with HIV are even more scarce than data in the general population. No published studies have reported a large series of patients with HIV and NAFLD who have undergone paired biopsies. Several studies have estimated the prevalence of liver fibrosis in broader groups of patients with HIV mono-infection using non-invasive markers. Among 432 patients with HIV mono-infection, advanced fibrosis was diagnosed in 8·3% of patients who were defined serologically by an aspartate aminotransferase-to-platelet ratio (APRI) of more than 1·5.[45] Independent predictors of considerable fibrosis included HIV viraemia and diabetes, perhaps suggesting the presence of NAFLD as an underlying cause. When transient elastography was used in a large cohort of patients with HIV, cirrhosis was discovered in only 1·1% of 1055 patients with asymptomatic HIV mono-infection who did not have a history of alcohol abuse.[46] However, the prevalence of steatosis or more moderate forms of fibrosis was not reported in this study. More recently, steatosis was assessed in a prospective cohort of 326 patients with HIV mono-infection or HIV–HCV co-infection by measuring the ultrasound-based controlled attenuation parameter (CAP) at baseline and at a 12 month follow-up. The proportion of patients with marked steatosis was not significantly different from baseline at 12 months (37% *vs* 39%, p=0·62).[47] Key predictors of steatosis included undetectable HIV viral load, high BMI, high fasting plasma glucose concentrations, and the use of raltegravir. However, detailed information about patients with HIV mono-infection and the assessment of NASH and fibrosis were not provided.

Published studies that report liver histology are generally limited to cross-sectional assessments. A matched case-control study found that patients with HIV-associated NAFLD were significantly more likely to have definitive NASH (63% *vs* 37%; p=0·04) and more features of liver injury (including lobular inflammation and acidophil bodies) than were patients with primary NAFLD.[48] Additionally, non-invasive markers of fibrosis, including the APRI and Fibrosis 4 (FIB4) score, were significantly higher in patients with HIV than in those with primary NAFLD, when controlling for age, sex, ethnicity, and BMI. This study raises the concern that perhaps patients with HIV and NAFLD are at high risk of disease progression. A smaller case-control study of patients with biopsy-proven NAFLD with and without HIV revealed similar liver histology, although those with HIV had a lower BMI and lower percentage fat mass than did patients with primary NAFLD, and they were also more physically active, further suggesting that NAFLD might be more severe or might have a more complex pathogenesis in patients with HIV.[31] Although some data about steatosis progression have been reported in studies that have analysed paired biopsy samples from patients with HIV–HCV co-infection, these studies were largely in the context of HCV treatment trials and do not include a description of findings relevant to NASH, which is the major driver of disease progression in this population.[49,50]

Impact of NAFLD on non-liver-related outcomes

NAFLD is the hepatic manifestation of a multisystem disease. Thus, in the general population, patients with NAFLD have an increased risk of coronary disease,

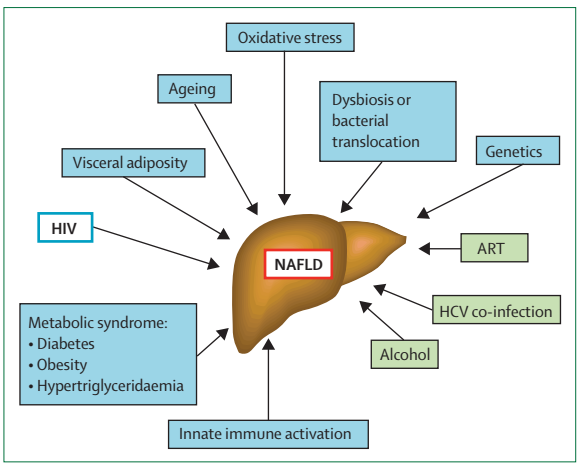

Figure 1: **Diagram of the multifactorial pathogenesis of NAFLD in patients with HIV**
Blue indicates primary causes and green indicates secondary causes. ART=antiretroviral therapy. HCV=hepatitis C virus. NAFLD=non-alcoholic fatty liver disease.

obstructive sleep apnoea, chronic kidney disease, cancers including hepatocellular carcinoma and colorectal cancer, and all-cause mortality compared with populations who do not have NAFLD.[51–54] Although patients with NASH, NAFLD-related fibrosis, or both have increased liver-related mortality compared with those who do not have these conditions, the most common cause of death in patients with NAFLD of any stage is cardiovascular disease.[3,51,54] This association between NAFLD and coronary artery disease has also been suggested in patients with HIV. In a series of 223 patients with treated HIV who underwent CT imaging to obtain coronary artery calcium scores, NAFLD (as measured by the CT liver-to-spleen ratio) increased the odds of a patient having excess coronary calcium deposition by almost four times, when controlling for age and the presence of hypertension.[55] Additional data are needed to establish how these findings relate to clinical cardiovascular outcomes. However, the diagnosis of NAFLD could be considered as a part of the metabolic monitoring and risk stratification used to optimise cardiac risk profiles in this high-risk population.

Pathogenesis of NAFLD in HIV

As in patients without HIV,[56] the accumulation of excess fatty acids in the liver, and the progression to hepatocyte injury, inflammation, and fibrosis in patients with HIV, are part of an incredibly complex process that has no single pathophysiological mechanism (figure 1). Patients with HIV are likely to be at a particularly high risk owing to the ageing of this population, their over-representation of traditional NAFLD risk factors, baseline disturbance of the gut–liver axis, and the additional impact of HIV infection and ART-related mechanisms.

Secondary causes of steatosis: ART, HCV, and alcohol

The traditional definition of NAFLD excludes secondary causes of hepatic steatosis, some of which are common in patients with HIV (eg, drug-induced, HCV-associated, and alcohol-induced steatosis). Several ART agents, particularly nucleoside reverse transcriptase inhibitors (NRTIs) and early-generation protease inhibitors, have been associated with steatosis and liver injury, and also with promotion of hypertriglyceridaemia, insulin resistance, and increased visceral adiposity.[57–59] Additionally, the dideoxynucleoside analogues didanosine and stavudine have been associated with mitochondrial injury that leads to microvesicular steatosis[12–18] and severe liver injury; due to these toxicities, these agents are now rarely used. Most of the literature from the modern ART era has not found a consistent association between an ART agent or treatment duration and the presence of NAFLD, and considerably more attention is now paid to the metabolic consequences of regimen choice (table). Additionally, HCV is now treatable in almost all cases, and other postulated secondary causes such as malnutrition are rare in patients with treated HIV. Thus, these secondary factors are likely to play a less prominent role in NAFLD pathogenesis in the future.

Alcohol consumption and high rates of excessive drinking are significantly more common among patients with HIV than the general population, and are associated with decreased ART adherence and reduced viral suppression.[60–64] Additionally, alcohol use patterns might be predictive of serological evidence of advanced liver disease among patients with HIV mono-infection and in those with HIV–HCV co-infection.[65,66] However, histological patterns of liver injury in patients with NAFLD and those with alcoholic hepatitis are indistinguishable, and the definition of NAFLD requires the absence of substantial alcohol intake. Although alcohol abstinence is generally recommended when NAFLD is diagnosed, what constitutes substantial or hepatotoxic levels of alcohol consumption remains uncertain. For the purposes of trial enrolment, substantial alcohol intake is usually defined for a 2-year period as more than 21 drinks per week in men and more than 14 drinks per week in women, although definitions in the literature vary considerably.[3] Cross-sectional studies indicate a possible synergistic effect of substantial alcohol use and excess bodyweight or diabetes on liver outcomes in the general population;[66–69] however, controversy exists as to whether light or moderate alcohol intake could have a paradoxically protective impact on liver disease and cardiovascular outcomes.[70] Thus, many important questions about this relationship remain unanswered. No studies have systematically examined the effects of various levels of alcohol consumption on the natural history of NAFLD among patients with HIV, but because alcohol intake is a potentially modifiable risk factor, recommending that patients avoid excessive alcohol consumption is an important part of NAFLD treatment.[3]

Metabolic syndrome, hyperlipidaemia, and diabetes

Obesity and metabolic syndrome might affect an increasing proportion of patients with HIV.[71] The prevalence of metabolic syndrome has markedly increased from 19·4% in the period from 2000 to 2001 to 41·6% in the period from 2006 to 2007 in the population studied by the multicentre D:A:D study group.[72] However, as in the general population, the prevalence of metabolic syndrome varies considerably (ranging between 14% and 42%) owing to factors including geography, sex, age, race, and the definition of metabolic syndrome that is used.[73–78] Overall, the prevalence of metabolic syndrome in patients with HIV is often reported to be similar to that in populations without HIV, especially when prevalence is adjusted for BMI.

When metabolic syndrome is present in patients with HIV, the most common feature seems to be dyslipidaemia, and few patients with HIV and features of metabolic syndrome meet the waist-circumference criterion for this condition.[73,77,79] The overall prevalence of features of metabolic syndrome in well characterised patients from 32 centres who were receiving ART was 18%, although 49% had at least two features but were not classified as having metabolic syndrome because they did not meet the waist circumference or waist-to-hip ratio criteria.[77]

Dyslipidaemia in patients with HIV and metabolic syndrome seems to be an effect of both HIV infection and ART.[80–83] Before ART was available, these patients were reported to have multiple abnormalities in their plasma lipid profiles, including increased concentrations of triglycerides and reduced concentrations of total cholesterol, LDL, and HDL.[57,84] In cohorts of treated patients, elevated concentrations of plasma triglycerides, a rise in HDL concentrations (although not to healthy concentrations) and a progressive increase in LDL concentrations are the most common abnormalities. However, an important factor to consider is that ART agents could have very different effects on lipid profiles when used individually compared with when they are used in combination, making it difficult to establish which drugs are having which effects. Two large cohorts of patients with HIV in the USA (namely, the Women's Interagency HIV Study and the Multicenter AIDS Cohort Study [MACS]) were recently surveyed for cardiovascular risk factors.[79] Both men (n=931) and women (n=1455) with HIV who did not have established coronary disease were more likely be on lipid-lowering agents and have high LDL, low HDL, and high triglyceride concentrations than were individuals without HIV. This dyslipidaemia seems to be more common in patients with HIV even though these patients were less likely to be overweight or obese than were individuals without HIV.[79,85] Whether treatment of dyslipidaemia affects NAFLD risk or disease progression remains to be determined.

The incidence of diabetes among patients with treated HIV also varies considerably depending on population demographics and the definition of diabetes that is used.[86] In the pre-ART era, the incidence of diabetes among patients with treated HIV was thought to be quite low (approximately 2% in treatment-naive patients).[87] In the modern ART era, the incidence of diabetes following ART initiation is probably higher overall among patients with HIV than in the general population, although the reported incidence still varies between cohorts. For example, the incidence of new-onset diabetes among the 33 389 patients with treated HIV in the D:A:D cohort was lower (5·72 per 1000 person-years of follow-up)[88] than that found in the MACS cohort (47 and 14 per 1000 person-years of follow-up among individuals receiving or not receiving ART, respectively).[89] Whether the incidence of new-onset diabetes is higher among patients with HIV than in control populations without HIV remains controversial,[89,90] but the MACS cohort study found that the increase in the relative risk of incident diabetes in patients with HIV who were on ART was nearly four times higher (10% over 4 years) than in controls who did not have HIV (3%).[89] Increasing age, weight, race, cumulative exposure to ART (particularly NRTIs), and dyslipidaemia were associated with the risk of diabetes in these cohorts.[86] Additionally, patients with lipodystrophy or excess visceral adipose tissue (VAT) might be at a particularly high risk of incident diabetes.[91–94] In one case-control study, diabetes and impaired glucose tolerance were found in 7% and 35% of patients with HIV-associated lipodystrophy, respectively, compared with in 0·5% and 5% of controls who did not have HIV but were matched for age and BMI.[93]

Thus, although metabolic syndrome and its components are consistently reported as risk factors for NAFLD among patients with HIV (table), their prevalence and incidence vary considerably, and they might account for only a proportion of the risk in this population.

Visceral adiposity and lipoatrophy

In addition to the high prevalence of metabolic syndrome in patients with HIV, specific changes in fat distribution—including increased VAT and peripheral lipoatrophy—have been under investigation in patients with HIV since shortly after the introduction of ART in the mid-1990s.[95,96] Although such changes in fat distribution were initially thought to be one syndrome (termed lipodystrophy) that was attributable to the side-effects of medication, evidence now indicates that specific changes in fat distribution represent separate processes with different complex pathophysiological mechanisms.[96–101] Peripheral lipoatrophy is both a direct consequence of chronic HIV infection and the result of specific ART agents, including thymidine analogues.

Conversely, increased visceral adiposity might be mostly the result of treated HIV, restoration of health, and the natural ageing process. However, VAT accumulation varies considerably among cohorts of treated patients, implying that simply achieving viral suppression and improved health might not be the only underlying mechanism.[100] The impact of NRTIs and protease inhibitors on metabolic

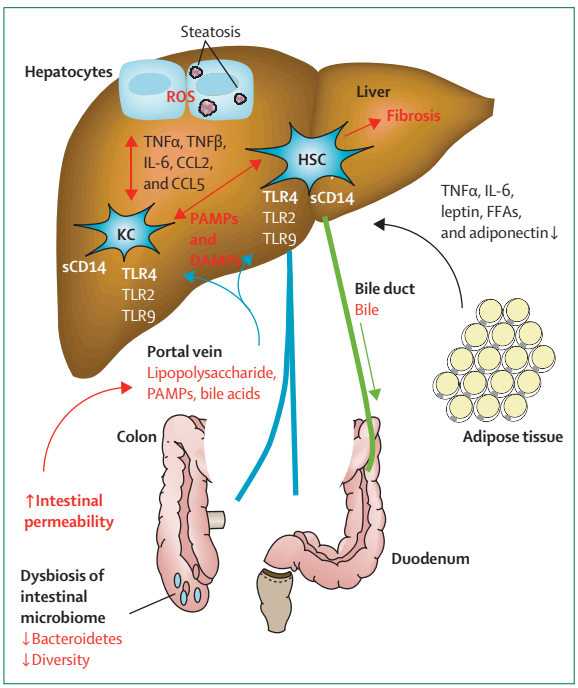

Figure 2: **The gut–liver axis in the pathogenesis of non-alcoholic fatty liver disease**

HIV, obesity, and metabolic syndrome are associated with dybiosis and decreased diversity of the intestinal microbiome. This change, along with changes in mucosal immunity in the setting of HIV, leads to increased permeability of the intestinal mucosal barrier and translocation of bacterial PAMPs, including lipopolysaccharide, into the portal vein. These molecules, along with liver-derived DAMPs, activate hepatic macrophages (ie, Kupffer cells) and also hepatic stellate cells through pathogen recognition receptors, including TLRs. This leads to the production of a cascade of inflammatory profibrotic cytokines that predispose to fatty acid accumulation, inflammation, and fibrosis. Cytokines from adipose tissue further contribute to this process and to insulin resistance. CCL=chemokine (C-C motif) ligand. DAMP=damage-associated molecular pattern. FFAs=free fatty acids. HSC=hepatic stellate cells. KC=Kupffer cells. NAFLD=non-alcoholic fatty liver disease. PAMP=pathogen-associated molecular pattern. ROS=reactive oxygen species. sCD14=soluble CD14. TLR=Toll-like receptor. TNFα=tumour necrosis factor α. TGFβ=transforming growth factor β.

syndrome components and visceral adiposity has been studied extensively, and evidence indicates that these medications can promote dyslipidaemia and insulin resistance. However, when combination treatment with protease inhibitors and non-NRTIs was compared with either treatment alone in a randomised trial, changes in abdominal and limb fat were similar across treatment groups.[102] Additional risk factors for central fat deposition include female sex, and greater baseline body fat and plasma triglyceride concentrations, highlighting the influence of metabolic predisposition.[103]

Although the incidence of lipodystrophy is thought to be declining alongside the declining use of NRTIs, its prevalence remains relatively high, because effective treatment strategies are scarce. The absence of simple and clinically useful criteria for increased VAT or HIV-associated disorders of fat partitioning that can differentiate this syndrome from the heterogeneous patterns of fat distribution seen in the general population has considerably limited the study of these conditions. These fat distribution changes could be characterised as part of the spectrum of metabolic syndrome, because visceral adiposity is strongly associated with the development of dyslipidaemia and diabetes. However, the effects of the HIV infection and long-term exposure to ART probably further enhance these changes. The specific ways in which the HIV-associated syndrome differs from metabolic syndrome, and how HIV-associated hepatic fat accumulation and liver injury differ from that seen in patients without HIV, are not known.

The gut–liver axis

The gut–liver axis has been strongly implicated in the pathogenesis of NAFLD and NASH both in animal models and in human beings.[104–112] This axis includes the intestinal microbiome; the intestinal barrier; the mucosal immune system; the mesenteric venous system, which drains directly into the portal vein; the liver; and enterohepatically circulating molecules, including bile acids (figure 2). This model suggests that during obesity and chronic liver disease, the changes that occur in the intestinal microbiome and in the host response to the microbiome, and increased intestinal permeability—which leads to translocation of bacterial products and endotoxin into the portal venous system—all contribute to hepatic steatosis, inflammation, and fibrosis. Additionally, the model suggests that alterations in the metabolism of nutrients—such as ethanol and choline—by the microbiome contribute to NAFLD pathogenesis.

Patients with HIV might be at a particularly high risk of gut-related mechanisms of liver injury as a result of HIV-related reductions in the diversity of the composition of the intestinal microbiome; this diversity is not completely restored by ART.[113–116] Additionally, strong evidence supports the role of alterations in mucosal immunity and increased intestinal permeability in the pathogenesis of chronic microbial translocation and immune activation in patients with HIV, and even those on ART.[117–121] Elevations in the concentrations of circulating endotoxin and soluble CD14 (a marker of chronic monocyte activation) have been associated with the severity of liver disease among patients with HIV–HCV co-infection,[122,123] and with visceral adiposity in patients with HIV mono-infection.[124] Although HIV-associated changes in the gut–liver axis are likely to further predispose these patients to the development and progression of NAFLD, no published studies have specifically linked the gut microbiome and bacterial translocation to this process in patients with HIV, and this could be an important area for future work.

Genetics

Several genetic polymorphisms have been associated with NAFLD risk in genome-wide association studies in the general population.[125] Among the best described are

polymorphisms of the *PNPLA3* gene, which are associated with increased NAFLD risk and increased disease severity.[126,127] The impact of *PNPLA3* polymorphisms on NAFLD risk has also been observed in small cohorts of patients with HIV.[26,29] Although the magnitude of this association and the exact physiological role of PNPLA3 in the liver remains unclear, genetic susceptibility is likely to play an important role in patients with HIV.[128]

Direct impact of HIV

HIV infection itself is also implicated in the development of metabolic syndrome[129] and therefore risk of hepatic steatosis. The degree of HIV viraemia has been associated with hypertriglyceridaemia, dyslipidaemia, and insulin resistance in patients with untreated HIV,[87,130] and HIV-associated mitochondrial damage has been implicated in systemic immune activation in the pathogenesis of diabetes.[131] Additionally, the virus might promote hepatic steatosis by interacting with sterol regulatory element-binding-protein 1 and peroxisome proliferator-activated receptor γ, which are key regulators of lipogenesis and insulin signalling, respectively.[132] Evidence indicates that HIV influences the activation of hepatic stellate cells, and thus causes hepatic collagen deposition and fibrogenesis.[133,134] Finally, although not well studied in the patients with HIV mono-infection, preliminary evidence indicates that HIV treatment with viral suppression might decrease the risk of steatosis development and progression.[33,135,136] In a study of 222 patients with HIV–HCV co-infection—which involved the assessment of paired liver biopsy samples to identify risk factors for steatosis progression—cumulative exposure to ART between biopsy samples and high CD4+ T-cell counts were associated with reduced progression of steatosis.[33]

Diagnostic evaluation

NAFLD is defined as evidence of hepatic steatosis, either by imaging or by histology, that is not associated with factors known to cause secondary hepatic fat accumulation such as considerable alcohol consumption, use of steatogenic medication, or hereditary disorders.[3] However, additional staging is essential for prognosis and treatment, because patients with NASH, fibrosis, or both are those who seem to be at considerable risk of disease progression. Unfortunately, the gold standard diagnostic tool remains liver biopsy, because no validated non-invasive tests can definitively differentiate NASH from simple steatosis, stage fibrosis, and investigate for competing causes of liver injury.

Given the inherent risks and diagnostic limitations of liver biopsy, especially in the widespread assessment of NAFLD, a considerable amount of research has focused on developing and validating both serological and imaging techniques to quantify each aspect of the disease spectrum: specifically, fat content, necroinflammation, and fibrosis. Although several non-invasive serological or combination assessments now exist for steatosis (eg, SteatoTest and the fatty liver index),[137–139] NASH (eg, cytokeratin 18 and NashTest),[51,139,140] and NAFLD-related fibrosis (eg, NAFLD fibrosis score, FIB4, and APRI),[51,139,141,142] none of these assessments has been extensively studied or validated against histology findings in patients with both NAFLD and HIV.[24,48,139,143–145]

Imaging techniques are becoming the preferred method to precisely quantify hepatic fat (eg, ultrasound-based CAP measurement, magnetic resonance spectroscopy [MRS]) and assess fibrosis (eg, ultrasound or magnetic resonance elastography),[51] although these modalities are not yet widely available. Ultrasound has advantages, including a lower cost, but might be more operator dependent than other imaging techniques, and it could have limited diagnostic yield in patients with poor acoustic penetration due to body habitus. In general, combinations of serological and imaging tests could provide the best estimates of disease severity; calculation of the NAFLD fibrosis score could be paired with imaging to estimate both fat fraction and liver stiffness, but unfortunately none of these serological and imaging assessments can replace liver biopsy as a definitive assessment when NASH or fibrosis is suspected.

Recommendations state that liver biopsy can be considered for patients with NAFLD who are at increased risk of having steatohepatitis and advanced fibrosis, risks that could be identified by the presence of metabolic syndrome or an elevation in the NAFLD fibrosis score, or when diagnostic uncertainty exists regarding co-existing chronic liver disease.[3]

Thus, all patients with chronically increased liver test panel results should be investigated for the presence of steatosis and then further risk-stratified using non-invasive assessments of fibrosis (figure 3). Exclusion of other forms of chronic liver disease and secondary causes of steatosis is an essential part of this investigation, and could include testing for viral hepatitis and taking a detailed history of alcohol consumption. Additionally, a proportion of patients with obesity and metabolic syndrome but normal plasma concentrations of liver enzymes will have NAFLD and perhaps even fibrosis.[146–149] Therefore, as data from patients with HIV accumulate, patients who have several NAFLD risk factors could reasonably be assessed for steatosis and fibrosis even if they have normal liver test results.

Treatment of NAFLD

An improved understanding of the complex pathogenesis of NAFLD has enabled the identification of many therapeutic approaches, including weight loss, decreasing fatty acid accumulation, decreasing inflammation and oxidative stress, inhibiting or resolving fibrosis, and manipulating the intestinal microbiome.[150,151] Most recommendations are based on studies in patients with NAFLD who do not have HIV, and since most studies

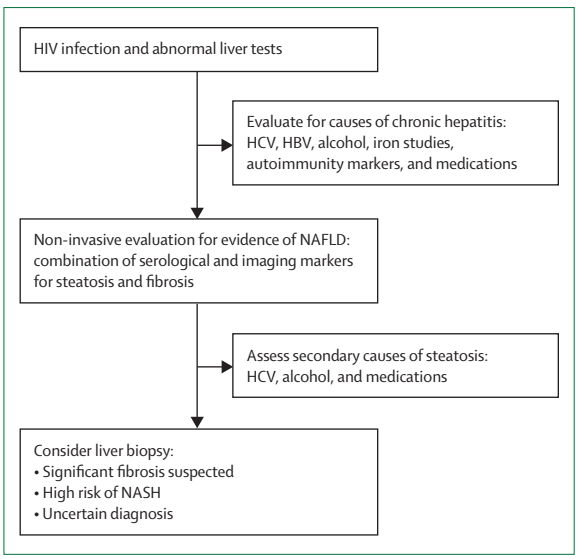

Figure 3: **Diagnostic approach for patients with HIV and suspected NAFLD**
HBV=hepatitis B virus. HCV=hepatitis C virus. NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic steatohepatitis.

include only short-term follow-up, long-term safety and efficacy data for therapeutic interventions are not available. General recommendations specific to patients with HIV include ensuring adequate suppression of viral load and modification of the ART regimen to avoid agents with a negative impact on the patients' metabolic profile if possible. Avoidance of stavudine and didanosine is preferable, and all patients with HIV–HCV co-infection should be treated for HCV.

Lifestyle interventions

Sustained weight loss through diet and exercise is the first-line treatment for NAFLD, and up to 10% reduction in weight is required for substantial histological improvement in necroinflammation.[3] Unfortunately this weight loss is rarely achieved without additional intervention, and the impact of lifestyle modifications on NAFLD among patients with HIV has not been established. Reduced alcohol consumption should also be strongly recommended, as should sufficient control of diabetes and components of metabolic syndrome.

Medical therapies

If liver test results do not considerably improve following lifestyle interventions, the recommended first-line therapy for patients without diabetes who have biopsy-proven NASH is vitamin E. This recommendation is based on several trials, including the randomised controlled PIVENS trial,[152] which compared the impact of vitamin E, pioglitazone, or placebo treatment on liver histology in 247 patients without diabetes or cirrhosis who had biopsy-proven NASH. Patients given vitamin E 800 IU daily for 96 weeks were significantly more likely to achieve a reduction of at least 2 points in the NAFLD activity score (NAS) than were patients given placebo (42% *vs* 19%, p<0·001). However, given the criteria for entry into studies of the efficacy of vitamin E in NASH, the impact of vitamin E in patients with diabetes, cirrhosis, NAFLD without NASH, or HIV is uncertain. Additionally, concerns have been raised about the safety of long-term vitamin E use, including in meta-analyses reporting increased all-cause mortality among patients on high-dose vitamin E[153–155] (although other studies have not found this association[156,157]) and perhaps an increased risk of prostate cancer.[158] These risks must be weighed against the potential benefits for each individual patient. With new therapies now possibly on the horizon, vitamin E might soon be used less frequently. In the PIVENS trial, pioglitazone use also improved liver histology, although only 34% of patients achieved at least a 2-point reduction in the NAS. Additionally, the long-term safety and efficacy of pioglitazone in patients without diabetes is not well established.

Although few effective pharmacological interventions are available, many clinical trials are investigating treatments for steatosis, steatohepatitis, and NAFLD-related fibrosis, and several agents are now in phase 3 clinical trials.[150,159–162] Obeticholic acid—a bile acid derivative that is a potent activator of the farnesoid X nuclear receptor (FXR) and was recently approved for use in patients with primary biliary cirrhosis—has shown promising efficacy in patients with biopsy-proven NASH.[163] When bound to FXR, obeticholic acid promotes insulin sensitivity, decreases hepatic gluconeogenesis, and decreases circulating concentrations of triglycerides, and it has thus been tested in various clinical settings, including in patients with NAFLD. In a phase 2 trial[163] in which patients were randomly assigned to groups receiving 72 weeks of either 25 mg obeticholic acid or placebo daily, those who received obeticholic acid were significantly more likely to achieve a 2-point reduction in the NAS without worsening fibrosis than were patients who received the placebo (45% *vs* 21%, p<0·0001). A larger phase 3 trial is now ongoing (NCT02548351); however, no data on the use of obeticholic acid in patients with HIV have been published to date.

Pilot studies investigating the use of rifaximin to alter the gut microbiota and diminish the translocation of bacterial components, including endotoxin, have been reported both in patients with NAFLD or NASH who do not have HIV[164] and in patients with HIV who do not show an immune response to ART.[165] These studies have shown only modest changes in the levels of markers of bacterial translocation in the short term, although manipulation of the microbiome in both disease states is of great interest.

Additionally, at least two ongoing clinical trials are investigating treatments for NAFLD specifically in patients with HIV (NCT03296831, NCT02684591). Tesamorelin, a synthetic growth-hormone-releasing hormone, is FDA approved for the treatment of excess

visceral adiposity in patients with HIV.[166] Tesamorelin is administered by subcutaneous injection and induces the pulsatile secretion of growth hormone. In a small randomised trial to assess the impact of tesamorelin on hepatic fat content, 60 patients with HIV received either 2 mg tesamorelin or placebo daily for 12 months.[167] Hepatic fat content was modestly but significantly reduced, as quantified by MRS, and visceral adiposity was also significantly reduced in patients receiving tesamorelin compared with those receiving the placebo.[167] A larger multicentre trial investigating the efficacy of tesamorelin in patients with HIV-associated NAFLD is now ongoing (NCT03296831). Additionally, arachidyl amido cholanoic acid, a fatty acid–bile acid conjugate that both decreases fatty acid synthesis and increases hepatic cholesterol efflux, has been shown to decrease hepatic fat content, as measured by MRS, in a small trial of patients with NAFLD.[168] Arachidyl amido cholanoic acid is now entering a phase 2B trial in patients with NAFLD and HIV (NCT02684591). Finally, the CCR2/CCR5 antagonist cenicriviroc, a novel HIV treatment that inhibits viral entry,[169] is now also in early trials for the treatment of NAFLD (NCT02217475). Cenicriviroc could thus represent a novel approach to treating or preventing NAFLD among patients with HIV and multiple NASH risk factors.

Ultimately, combination therapies that target the specific pathology observed in each individual patient is likely to be required to optimise outcomes. This will include modifying secondary causes of steatosis with particular consideration of an individual patient's phenotype—ie, whether the patient is obese or lean, and insulin-resistant or normoglycaemic, and whether the patient has steatosis or steatohepatitis, and fibrosis or no fibrosis.

Conclusions and future directions

Although NAFLD is clearly common in patients with HIV and results from a complex array of pathophysiological mechanisms, many essential unanswered questions remain to be addressed. Very little is known about the pathogenesis of NAFLD in patients with HIV and the extent to which HIV, ART, and metabolic syndrome account for its excess prevalence. The natural history of NAFLD in this population and the impact of NAFLD on liver-related and non-liver-related mortality require additional study. We urgently need to develop and validate accurate non-invasive biomarkers and imaging assessments of hepatic fibrosis in patients with HIV to facilitate accurate diagnosis and staging on a large scale. This is especially important given the emergence of obesity and metabolic syndrome in this population, and the likelihood that NAFLD will contribute to an increasing proportion of non-AIDS-related deaths (ie, deaths due to progressive liver disease, and associated conditions such as cardiovascular disease and cancer). Finally, broader enrolment of patients with HIV in treatment trials for NASH and NAFLD-related fibrosis will be essential. Although the scarcity of therapeutic options might have discouraged NAFLD diagnosis and staging until now, the large number of novel treatment strategies in clinical trials, some of which are in late phases, should make NAFLD diagnosis and staging a priority, especially in high-risk groups such as individuals with HIV.

Search strategy and selection criteria

References for this Review were identified by searching PubMed using the search terms "NAFLD", "fatty liver", "NASH", "steatosis", "fibrosis", "human immunodeficiency virus", and "HIV". The search was restricted to studies published between January, 1985, and June, 2016. Articles were also identified through searches of my own files and the reference lists of the articles identified by the abovementioned literature search. Only papers published in English were reviewed.

Contributors

I was responsible for the research and preparation of this manuscript in its entirety.

Declaration of interests

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