HHS Public Access

Author manuscript

Curr HIV/AIDS Rep. Author manuscript; available in PMC 2019 June 01.

Published in final edited form as:

Curr HIV/AIDS Rep. 2018 June ; 15(3): 212–222. doi:10.1007/s11904-018-0392-1.

NAFLD and HIV: Do Sex, Race, and Ethnicity Explain HIV-Related Risk?

Subada Soti[1], **Kathleen E. Corey**[2], **Jordan E. Lake**[3], and **Kristine M. Erlandson**[4]

[1]University of Colorado-Anschutz Medical Campus; School of Medicine; Aurora, CO

[2]Massachusetts General Hospital and Harvard Medical School; Boston, MA

[3]University of Texas Health Sciences Center; Houston, Texas

[4]University of Colorado-Anschutz Medicine Campus; Department of Medicine, Division of Infectious Diseases; Aurora, CO

Abstract

Purpose—Here, we review the epidemiology, diagnosis, and management of NAFLD in the general population, discuss HIV-specific differences in NAFLD pathogenesis, and summarize what is known regarding differences in NAFLD by race/ethnicity and sex.

Recent findings—The reported prevalence of NAFLD among people living with HIV varies by age, body mass index, comorbidity, and method of NAFLD diagnosis, but is generally thought to be greater among HIV-infected compared to -uninfected populations. Minorities and women tend to experience poorer HIV treatment outcomes (1–5), and are at the greatest risk for significant weight gain with HIV treatment (6). Thus, woman and minorities living with HIV may be at a higher risk of developing NAFLD and progressive liver disease.

Summary—Disparities in the diagnosis, progression, and prognosis of NAFLD and HIV-associated NAFLD may be, in part, explained by genetic and sex differences however data is limited.

Keywords

nonalcoholic fatty liver disease; NAFLD; HIV-associated NAFLD; HIV complications; review

Author Contact Information: Kristine M. Erlandson, 12700 E. 19th Avenue; Mail Stop B168; Aurora, CO 80045, Phone 303-724-4941; Fax 303-724-4926, Kristine.erlandson@ucdenver.edu.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Subada Soti and Kathleen E. Corey declare no conflict of interest.

Jordan E. Lake has served as a consultant to Merck and receives research funding from Gilead Sciences.

Kristine M. Erlandson has received research funding (paid to the University of Colorado) from Gilead Sciences, and has served as a consultant to Gilead Sciences, EMD Serono, and Theratechnologies.

Epidemiology of NAFLD

Non-alcoholic fatty liver disease (NAFLD) is characterized by steatosis (>5% of hepatocytes with lipid droplets), in the absence of other secondary causes of steatosis (7) including alcohol use (8). Worldwide, the prevalence of NAFLD has risen since first described in 1980, paralleling the increase in obesity, diabetes, and the metabolic syndrome (9). Currently, NAFLD is the most common etiology of chronic liver disease, affecting approximately 25% of the population worldwide (10), and between 17–51% of the US population (7, 11–13). A subset of individuals with NAFLD develop non-alcoholic steatohepatitis (NASH), the progressive form of NAFLD. NASH is characterized by the presence of both steatosis and cellular injury, with the latter manifested as hepatocyte ballooning and lobular inflammation. Hepatic fibrosis can also develop with NASH, facilitating progression to cirrhosis, decompensated liver disease and hepatocellular carcinoma. In the United States, NASH is the second leading indication for liver transplantation (14), and the most common indication for those under age 50(15).

Obesity, central adiposity, type 2 diabetes mellitus (T2DM), insulin resistance, and dyslipidemia are strongly associated with, and well-established risk factors for the development of both NAFLD and NASH (Table 1). Indeed, the prevalence of these risk factors is high in NAFLD and higher in NASH with obesity among 51% of NAFLD and 82% of NASH patients, T2D among 23% and 44%, and dyslipidemia among 69% and 72%, respectively (10). NAFLD is also present in a small percentage of lean individuals (body mass index [BMI] < 25 kg/m^2): in the National Health and Nutrition Examination Data, 7% of non-obese individuals had NAFLD compared to 28% in obese individuals (16).

Diagnosis of NAFLD

As NAFLD is often asymptomatic (17), it is most commonly diagnosed incidentally during abdominal imaging performed for other indications, or by elevated liver enzymes tests during routine laboratory testing. The presence of hepatic steatosis can be identified with a variety of imaging techniques including ultrasound, computed tomography (CT) scan, vibration controlled transient elastography (VCTE or Fibroscan®) with controlled attenuation parameter (CAP), magnetic resonance (MR) imaging, MR spectroscopy (MRS) or MR imaging proton density fat fraction (MRI-PDFF) (18–20). However, although several advanced modalities are in development, these currently available imaging tests only identify steatosis and cannot distinguish steatosis alone from NASH.

A number of serum biomarkers for NASH have been tested including alanine aminotransferase (ALT), adiponectin, CK18 M30, leptin, and HOMA-IR, that, although associated with various pathophysiological mechanisms of liver damage, have limited (<80%) sensitivity and specificity for NAFLD versus other causes of liver disease or metabolic disturbance (21). The NAFLD Liver Fat Score predicts the presence of NAFDL with a sensitivity of 86–95% and specificity of 51–71%, depending on the score cut-off value, and includes the presence of metabolic syndrome, T2DM, fasting serum insulin, fasting serum aspartate aminotransferase (AST), and AST/ALT ratio (22).

As no serum biomarkers or imaging studies can currently distinguish steatosis alone from NASH, liver biopsy remains the “gold standard” for the diagnosis of NAFLD, NASH and for fibrosis staging (7). In addition to providing a definitive diagnosis of NAFLD, liver biopsy allows the evaluation of concurrent liver diseases such as hemochromatosis and autoimmune hepatitis and distinguishes between steatosis and NASH. Thus, liver biopsy is vital in ensuring the correct diagnosis, and for ongoing surveillance: patients with stage 3–4 fibrosis have increased risk for hepatocellular carcinoma and should undergo routine screening for hepatocellular carcinoma. Similarly, patients with NASH and/or fibrosis warrant evaluation for intensive medical management, weight reduction surgery, and clinical trial enrollment, where appropriate. Liver biopsy, however, is an invasive procedure and not without risk: serious complications occur in approximately 1% of patients and include infection, injury of other organs, bleeding, and rarely death (23, 24). Additionally, biopsy is expensive and subject to sampling error and observer variability(25). Hence, the development of non-invasive methods to diagnose NASH and fibrosis are of particular interest.

General Issues in the Management of NAFLD

Lifestyle modifications are the cornerstone for management of NAFLD and NASH. In a prospective cohort study of 12 months of lifestyle intervention weight reduction of at least ≥10% total body weight was associated with resolution of NASH in 90% of individuals and improvement in fibrosis by at least one stage in 45% (26). However, the ability to maintain weight loss beyond one year and the impact of weight regain on NASH histology is unknown. Routine physical activity (150–200 minutes per week) and the Mediterranean diet have also been shown to improve hepatic steatosis and are recommended for all individuals with NAFLD (27). However, as diet and exercise goals can be difficult for many patients to achieve and sustain (7), significant interest lies in the development of these pharmacotherapies to prevent and treat disease.

Interventions including vitamin E and pioglitazone have been investigated primarily for the treatment of biopsy-proven NASH, and have demonstrated variable efficacy (28–32). Among non-diabetics, vitamin E improves biopsy-proven NASH in a subset of patients, but has been associated with an increased risk of prostate cancer (33), hemorrhagic stroke (34) and a possible increase in all-cause mortality(32, 35). Pioglitazone has been associated with NASH resolution among both T2DM and non-diabetics (30, 32, 36). Concerns for significant weight gain (36), loss of bone mineral density (37), risk for exacerbation of congestive heart failure (38), and bladder, prostate, or pancreatic cancer (39) however, limit enthusiasm for pioglitazone in clinical practice. Clinical trials of novel therapies (i.e., obeticholic acid(40), tesamorelin [NCT03296831](41)), cenicriviroc [NCT02684591 and NCT03059446](42), OMACOR [NCT00760513](43), and elafibrinor [NCT01694849](44)), are underway.

NAFLD in HIV: Similarities and Differences

Liver disease is a frequent cause of death among HIV-infected persons in several large cohorts (45–48). Although viral hepatitis contributes to the majority of liver-related deaths among HIV-infected adults, the proportion of liver disease attributed to NAFLD is

increasing and expected to play an increasing role in liver-related morbidity and mortality. Due in part to differing antiretroviral exposure (i.e., older versus more contemporary therapy), method of NAFLD diagnosis (as in the general population), co-infection with hepatitis C or B virus, and screening of select populations (such as age-specific or sex-specific cohorts), the true prevalence of NAFLD and/or its contribution to progressive liver disease among HIV-infected populations varies considerably (Table 1)(49–59). However, NASH appears to be more common among individuals with NAFLD and HIV when compared to those with NAFLD but without HIV. A case control study compared 33 individuals with biopsy-proven NAFLD and HIV to 33 persons with biopsy-proven NAFLD without HIV. HIV-infected individuals were more likely to have NASH (37% vs. 63%, $P = 0.04$) and signs of liver injury on biopsy such as lobular inflammation (21% vs. 67%, $P < 0.001$) or acidophil bodies (15% vs. 64%, $P < 0.004$)(60).

Many risk factors for NAFLD in HIV-infected patients are reflective of underlying causes of NAFLD in the general population, including obesity, T2DM or insulin resistance, hypertension, and dyslipidemia. However, the prevalence of NASH not only appears to be higher among HIV-infected adults with NAFLD but present among persons without the typical NAFLD phenotype of metabolic syndrome. For example, in a small cohort of biopsy-proven NAFLD, participants with HIV had a lower BMI, lower fat mass, and greater self-reported physical activity than their HIV-uninfected counterparts despite a similar age, caloric intake, liver histology, and degree of insulin resistance (61). Furthermore, the higher ratio of visceral adipose tissue (VAT) to BMI may lead to higher prevalence of NAFLD among lean HIV-infected compared to -uninfected populations (62–64). Thus, additional mechanisms are hypothesized to contribute to NAFLD pathogenesis among those with HIV.

Many early antiretroviral therapy regimens, particularly the nucleoside reverse transcriptase inhibitors, were associated with mitochondrial toxicity through multiple proposed mechanisms, including polymerase-gamma inhibition and reduction in mitochondrial DNA. The resultant mitochondrial toxicity and impaired fatty acid oxidation is thought to play a major role in the ectopic fat deposition in other tissues and organs, including the liver, and in the development of lipodystrophy (65–68). Indeed, therapies such as stavudine and didanosine with the greatest mitochondrial toxicity were associated with the most pronounced effects in regard to lipodystrophy, pancreatitis, and hepatotoxicity. Both Price at al., 2015 and Guaraldi et al., 2008 found associations between nucleoside reverse transcriptase inhibitor use (OR 1.44 per 5 years, $P= 0.02$ and OR 1.12 per year, $P\leq0.001$, respectively) and hepatic steatosis (51, 57). A recent switch study from efavirenz to raltegravir-based therapy in HIV-infected patients with NAFLD resulted in significant improvement in hepatic steatosis by VCTE with CAP compared to patients who remained on efavirenz, suggesting that other antiretroviral regimens may have more of an effect on hepatic steatosis than previously recognized (69).

Beyond these specific antiretroviral therapies, most studies have not found an association between other HIV-specific characteristics and NAFLD prevalence. As shown in Table 1, the majority of recent studies have failed to find an association between severity of HIV disease (CD4+ T-cell count, HIV-1 RNA level, history of opportunistic infection), duration of HIV infection, or specific antiretroviral exposure and NAFLD presence or progression to NASH.

In contrast to epidemiologic studies, a recently published murine model of HIV VPR protein expression suggests that HIV-1 may indeed impact NAFLD. Expression of VPR or infusion of synthetic VPR into transgenic mice expressing the HIV-1 accessory protein VPR resulted in increased de novo lipogenesis, impaired fatty acid oxidation, increased liver triglyceride content, and elevated liver enzymes(70).

Development of NAFLD and progression to NASH is thought to be multifactorial, and while many of these contributors are not specific to HIV, many occur more frequently or to a greater extent among HIV-infected populations. Chronic inflammation and immune activation, for example, are hallmarks of HIV pathogenesis and underlie the development of many comorbidities associated with HIV. Increased adiposity is associated with increased systemic and tissue level inflammation in HIV, and inflammatory cytokine production from adipose tissue and/or intra-hepatic lipid accumulation may contribute to further hepatic fat deposition or progression to NASH and fibrosis (71). Indeed, elevated systemic inflammation (IL-6 and TNF-alpha levels) have been associated with development of fatty liver (72). A recent study within The Multicenter AIDS Cohort Study (MACS), however, found that higher inflammatory cytokine levels (Intercellular Adhesion Molecule [ICAM]-1, C-reactive protein, IL-6, soluble tumor necrosis factor receptor [sTNFR]2) were associated with greater CT-defined hepatic steatosis among HIV-uninfected but not HIV-infected men, despite higher levels of these markers among HIV-infected men. Of note, CT-based diagnosis of hepatic steatosis may underestimate the prevalence of mild-to-moderate NAFLD (73) and limit the ability to compare inflammatory biomarkers by disease severity. Several *post hoc* analyses of randomized, controlled studies and small biopsy studies in HIV-uninfected populations have suggested a role for the anti-inflammatory effects of statins in NAFLD, as evidenced by improvement in biochemical, histologic, and imaging measures (74). Limited data among HIV-infected populations have failed to find benefit on steatosis (by the liver fat score)(75); studies assessing CT or MRI-based measures may further clarify whether anti-inflammatory agents, such as statins, impact liver steatosis in HIV.

Systemic inflammation in HIV may be facilitated by disruption in the gut-liver axis in this population (76), which may be further affected by differences in the microbiome by NAFLD and by HIV serostatus or antiretroviral therapy (77–79). Disruptions in gut wall permeability and perturbations in the normal microbiome may further exacerbate hepatic inflammation and disrupt glucose metabolism and fatty acid oxidation, resulting in greater hepatic fat deposition or progression of hepatic steatosis (80, 81).

Considerations of Disparities in NAFLD and HIV: Do genetic or sex factors contribute to health disparities in NAFLD and HIV?

Regardless of comorbidities, minorities and women tend to experience later HIV diagnosis and poorer HIV treatment outcomes (1–5). Furthermore, minorities and women living with HIV have a greater prevalence of obesity and the greatest risk for significant weight gain with HIV treatment (6). Although socioeconomic factors may impact these differences, race, ethnicity, and sex further contribute to disparities in NAFLD among HIV-infected populations. Here, we will summarize what is known on the role of genetics and sex on

NAFLD risk in the general population, and then detail what is currently known in among persons living with HIV.

Similar to many other disease processes, disparities exist in the prevalence, progression, and prognosis of NAFLD. In the US, studies consistently show that Caucasians and Hispanics have the highest and African Americans have the lowest prevalence of NAFLD. Though the prevalence varies by study population, NAFLD prevalence among Hispanics ranges from 28 to 58% and African Americans from 11 to 35% (13). Globally, NAFLD, as diagnosed by imaging, follows similar racial/ethnic disparities, with South America and the Middle East having the highest prevalence of NAFLD at 30–32%, Asia at 27%, North America and Europe at 24%, and Africa with the lowest prevalence at 13% (10). A recent meta-analysis of 34 studies and nearly 370,000 patients further described a greater prevalence of NASH among Hispanics compared to Caucasians or Blacks, but no significant differences in the proportion of significant fibrosis by race/ethnicity (82). Studies on prognosis were limited and unable to be pooled, but suggested a greater odds of cirrhosis among Hispanics, and all-cause mortality among Blacks (82).

These differences may be partially explained by differences in lifestyle, body fat distribution, and co-morbidities, including T2DM, dyslipidemia, hypertension and the metabolic syndrome, that vary by race and ethnicity. For Hispanics, the higher prevalence of progression from NAFLD to NASH is overwhelmingly attributed to obesity and insulin resistance (13), and studies have shown a similar prevalence of hepatic steatosis between Hispanic and non-Hispanic Caucasians, when adjusted for total body fat (83, 84). In contrast, the low prevalence of NAFLD, NASH, and associated fibrosis in African Americans persisted even after adjusting for differences in BMI (83), insulin resistance, or ethanol ingestion (13). Since the low prevalence in African Americans does not appear to be completely explained by racial differences in risk exposure, this begs the question of the role of genetic differences.

In addition to the difference in prevalence, the rate of heritability of NAFLD also differs based on the race/ethnicity. According to large population studies, Hispanics have high heritability of NAFLD at 33%, Caucasians have 16–27% and African Americans 14% (85). Although some of these differences in prevalence and heritability could be due to cultural, lifestyle, or environmental factors, this again suggests an underlying genetic component in NAFLD and NASH risk.

Genetic Factors in the NAFLD Risk: Data from HIV-Uninfected and HIV-Infected Populations

Genetic differences in the risk for NAFLD or NASH progression in both the general population and among hepatitis C virus (HCV)-infected populations are well described (85–87). Many of these polymorphisms involve genes that are involved in inflammatory responses, metabolism, or mitochondrial haplotypes (87). The strongest and most consistent associations with the presence and progression of NAFLD in these populations has been with the rs738409 single nucleotide polymorphism (SNP) on the PNPLA3 gene(88, 89). The data on the role of rs738409 SNP on PNPLA3 gene among HIV/HCV co-infected or HIV

mono-infected populations is more limited, as reviewed below and in Table 2 (51, 53–55, 90).

Palatin-like phospholipase domain-containing protein 3 (PNPLA3) gene codes for adiponutrin or calcium independent phospholipase A2-epsilon that enables triglyceride hydrolysis in adipocytes. PNPLA3 has been associated with the presence of NAFLD and with progression to NASH and fibrosis development among HIV-uninfected populations in multiple studies, after accounting for BMI, T2DM, alcohol use, and ancestry (85, 88, 91). The GG genotype is associated with a greater accumulation of steatosis than the CC genotype, with up to 73% increase in percentage of steatosis (88, 89). Prior studies have shown that Hispanics, who have the highest prevalence of NAFLD, also have the highest prevalence of GG genotype (25%) and Blacks, with the lowest prevalence of NAFLD, have the lowest prevalence of GG genotype (2%)(91). A greater percentage of the GG genotype in some patient populations may explain similarities in NAFLD prevalence despite differences in obesity and metabolic syndrome: 13–19% of Asians have GG genotype while only 4% of Caucasians have GG genotype. These genetic differences may, in part, explain the similarity in prevalence of NAFLD between Asians and Caucasians (91).

The rs738409 SNP on the PNPLA3 gene may be most useful in predicting NAFLD prevalence and progression among non-obese populations. For example, among a Japanese cohort, a greater proportion of the rs738409 GG genotype was found among non-obese, NAFLD patients than among individuals with obesity and NAFLD. In a separate cohort in Italy, rs738409 was associated with a greater risk of disease progression among non-obese but not obese NAFLD patients (92).

The data on genetic differences among HIV-infected populations, specifically the role of PNPLA3 and the rs738409 SNP in NAFLD prevalence and severity, are summarized in Table 2. In the MACS, a cohort of men who have sex with men living with or at risk for HIV infection, found a strong association between PNPLA3 non-CC genotype and hepatic steatosis prevalence as defined by a liver-to-spleen attenuation ratio <1.0 on non-contrast CT among HIV-infected men (≤10% with HCV). In this cohort excluding heavy alcohol users, 19% of HIV-uninfected and 13% of HIV-infected men had hepatic steatosis and the proportion of PNPLA3 genotype did not differ by HIV serostatus. The non-CC genotype of PNPLA3 (rs738408) was associated with an increased odds of steatosis in the combined (HIV-infected and uninfected) cohort (OR 2.06; 95% CI 1.24, 3.33 p=0.005) and among HIV-infected men only (OR = 3.30, 95% CI 1.66, 6.57; P= 0.001), but not among HIV-uninfected men only (OR =1.14; 95% CI =0.51, 2.54; p=0.75), with a trend towards an interaction between HIV serostatus and PNPLA3 (51). Of note, CT-based estimates of hepatic steatosis have a lower sensitivity for detection of mild to moderate steatosis (73), thus prevalence of steatosis by CT-based estimates in the MACS is generally lower than prevalence among other cohorts of similar characteristics.

Results from other studies report a variety of findings, likely influenced by differences between studies characteristics including race/ethnicity, sex, co-infection with hepatitis B or C virus, alcohol use, HIV treatment history, and metabolic syndrome parameters. Among 62 HIV-infected adults at the National Institutes of Health clinic with elevated liver function

tests and without HCV co-infection (nearly 30% Hispanic), Morse, et al found a significant association between the rs2281135 and rs228115 SNP in PNPLA3 and increased ALT, steatosis grade, frequency of NASH, and fibrosis stage (54). Similar findings were seen in a cohort with HIV/HCV coinfection: Among 215 HIV/HCV co-infected patients with liver biopsy, the PNPLA3 rs738409 SNP was associated higher FIB-4 scores and the presence of fibrosis (55). Similarly, a separate study of 168 HIV/HCV co-infected patients with biopsy-proven NAFLD/NASH (all Caucasian, none with T2DM or insulin resistance) found a strong association between PNPLA3 and severe steatosis, independent of BMI, CD4+ t-cell count, liver enzymes, total cholesterol, antiretroviral regimen, and HCV genotype (93).

In contrast, findings from other HIV study populations do not support this association. Dold, et al. determined the frequency of several SNPs among 117 HIV-infected patients without active hepatitis B or C co-infection: none of the alleles of interest differed by NAFLD prevalence or fibrosis presence (94). Scheiner, et al also failed to find a significant association with PNPLA3 rs738409 and biopsy-proven fibrosis or steatosis among 177 HIV/HCV co-infected patients, and no difference in HCV treatment response by PNPLA3 genotypes (53). Furthermore, among 431 HIV-infected patients in Spain (64% with active HCV co-infection), Macias, et al failed to find a similar association with the PNPLA3 gene, but did find associations between SNPs in the LPPR4 and SAMM50 genes and NAFLD and NASH, respectively (59). Of note, many of these are small studies, and many include patients with HCV co-infection, thus generalizability of the results to HIV mono-infected populations are limited.

LPR4 gene codes for a protein in the Lipid Phosphate Phosphatase (LPP) family. LLP dephosphorylates and inactivates bioactive lipid metabolites of cellular function (95). HIV has been known to infect the hypothalamus and disturb its metabolic functions and LPR4 is expressed in axonal membranes, especially in the hypothalamus. This may explain an association between LPR4 with NAFLD in HIV (90). SAMM50 gene codes for a protein vital to the structure of the mitochondria (59). Several other SNPs have been associated with liver disease progression in HIV/HCV co-infection, without mention of underlying NAFLD/NASH (87). SNPs within the mitochondria, consistent with haplogroups HV and H were associated with slower fibrosis progression and haplotype U with faster progression in study of HIV/HCV co-infection, which may further support racial/ethnic differences linked to haplotype, but again, the role of these mitochondrial haplotypes in NAFLD and NASH without HCV are not established (96).

The Role of Sex in the NAFLD Risk: Data from HIV-Uninfected and HIV-Infected Populations

The impact of sex differences on the prevalence or progression of NAFLD among the general population is conflicting. Both the National Health and Nutrition Examination Survey (NHANES) and the Dallas Heart Study found that men (particularly white men), had nearly double the risk of NAFLD compared to women (9, 13, 57, 97). In contrast, other studies have found that women have greater prevalence of NAFLD in the setting of high visceral fat (98), and an Australian study found that adolescent girls are 1.5 times more likely than adolescent boys to have NAFLD (99). This conflicting data may be related, in part, to the presence of endogenous estrogens within visceral fat, or lower levels of estrogen

in adolescent girls. For example, estrogen in pre-menopausal women is associated with hepatoprotective effects including improved lipids and reduced fibrogenesis; these effects may be lost with menopause, and, in conjunction with visceral fat gains in menopause, contribute to NAFLD (100).

Other studies suggest that sexual dimorphism might affect gene variability on NAFLD: a meta-analysis including sixteen studies found a negative correlation between the proportion of men in studies and the observed association between the rs738409 SNP and liver fat content (88), such that as the proportion of men increased, the difference in liver fat content between alleles of rs738409 SNP on PNPLA3 gene decreased. Additionally, proteins such as SREBP-1c and liver X receptor that affect the expression of PNPLA3 gene (101) are modulated by estrogen (102), and a greater association between PNPLA3 rs738409 and NAFLD prevalence in HIV-uninfected women has been observed (26). As many prior studies did not adjust for pre or post-menopausal status, the influence of estrogen could explain conflicting reported data on sex differences. Lastly, the modality of NAFLD diagnosis differed between cohorts, and imaging accuracy may also vary by sex.

Data among HIV-infected populations is limited and similarly conflicting: in a recent analysis of 87 women and 142 men, with and without HIV infection from the San Francisco Women's Interagency HIV Study and the community, HIV-infected women had less steatosis than HIV-uninfected women after adjusting for demographics, lifestyle, and metabolic factors (50). No differences by HIV serostatus were detected among men in the fully adjusted models. In an Italian cohort with HIV, Guaraldi et al. found that male sex was associated with a greater odds of CT-defined NAFLD (OR 2.5; 95% CI 1.1, 5.8) compared to female sex, after adjusting for waist circumference (57). Multiple studies have suggested that men are at lower risk for progression to fibrosis, though the number of women and low fibrosis stages included in many of these studies limit conclusions (54, 56, 103, 104)

Do Genetic and Sex Differences Impact Clinical Care?

Even though genes such as PNPLA3 are strongly associated with NAFLD, the clinical utility of these genetic underpinnings have yet to be established, and routine screening is not recommended. Currently, genetic association utility is generally limited to use as a covariate in determining associations with NAFLD prevalence or disease severity in research settings, and most studies have not found a marked improvement in predictive accuracy with inclusion of genetic information. Larger studies utilizing genetic data and incorporating other "-omics" based outcomes may help to advance understanding of these underlying genetic factors. As race, ethnicity, and sex underlie some genetic differences, these factors may contribute to an understanding of disease progression or mortality due to NAFLD-associated comorbidities. For example, Blacks with NAFLD in the Multi-Ethnic Study of Atherosclerosis had a greater prevalence of abdominal aortic calcification compared to whites, suggesting that NAFLD-related metabolic disease may also vary by race and ethnicity (105), as NAFLD prevalence does. Similarly, among Chinese adults, the presence of NAFLD was associated with more pronounced differences in lipids and renal function in men than among women (106). Further studies on NAFLD prevalence and prognosis by race, ethnicity, sex, and HIV serostatus can better inform the diagnosis and management of

concomitant comorbidities, and understand the role that NAFLD plays in the development of these comorbid disease by race, ethnicity, and sex. Inclusion of adequate numbers of women in studies of NAFLD and HIV may help elucidate sex-based differences in NAFLD pathogenesis that may explain observed differences in prevalence and progression, including hormone-associated pathways. Lastly, very little is known regarding the prevalence and pathogenesis of NAFLD in transgender persons. Although pre-menopausal endogenous estrogen appear hepatoprotective among natal females, exogenous estrogen therapy among transgender persons worsens insulin sensitivity and increase inflammation, triglycerides, and subcutaneous and visceral adipose tissue (107–110).

Conclusion

In conclusion, with the drastic increase in NAFLD prevalence worldwide, there is a tremendous need for accurate scalable screening, prognosis, treatment prediction, and new interventions. Individuals living with HIV have unique risk factors for NAFLD but data on the prevalence of NAFLD and NASH and the impact of gender, race and ethnicity on these risk factors and NAFLD overall remain undefined. Further work is needed to understand the pathogenesis of NAFLD in HIV.

Acknowledgments

This work was supported by the National Institute on Aging of the National Institutes of Health (K23 AG050260 and R01 AG054366 to KME), the National Institute of Allergy and Infectious Diseases (K23 AI110532 to JEL) and the National Institute of Diabetes and Digestive and Kidney Diseases (K23 DK099422 to KEC).

The contents are solely the responsibility of the authors and do not necessarily represent the official views of NIH.

References

1. Meditz AL, MaWhinney S, Allshouse A, Feser W, Markowitz M, Little S, et al. Sex, race, and geographic region influence clinical outcomes following primary HIV-1 infection. J Infect Dis. 2011; 203(4):442–51. [PubMed: 21245157]
2. Beer L, Mattson CL, Bradley H, Skarbinski J. Medical Monitoring P. Understanding Cross-Sectional Racial, Ethnic, and Gender Disparities in Antiretroviral Use and Viral Suppression Among HIV Patients in the United States. Medicine (Baltimore). 2016; 95(13):e3171. [PubMed: 27043679]
3. Gant Z, Dailey A, Hu X, Johnson AS. HIV Care Outcomes Among Hispanics or Latinos with Diagnosed HIV Infection - United States, 2015. MMWR Morb Mortal Wkly Rep. 2017; 66(40): 1065–72. [PubMed: 29023431]
4. Millett GA, Peterson JL, Flores SA, Hart TA, Jeffries WLt, Wilson PA, et al. Comparisons of disparities and risks of HIV infection in black and other men who have sex with men in Canada, UK, and USA: a meta-analysis. Lancet. 2012; 380(9839):341–8. [PubMed: 22819656]
5. Wejnert C, Hess KL, Rose CE, Balaji A, Smith JC, Paz-Bailey G, et al. Age-Specific Race and Ethnicity Disparities in HIV Infection and Awareness Among Men Who Have Sex With Men--20 US Cities, 2008–2014. J Infect Dis. 2016; 213(5):776–83. [PubMed: 26486637]
6. Erlandson KM, Zhang L, Lake JE, Schrack J, Althoff K, Sharma A, et al. Changes in weight and weight distribution across the lifespan among HIV-infected and -uninfected men and women. Medicine (Baltimore). 2016; 95(46):e5399. [PubMed: 27861378]
7. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology (Baltimore, Md). 2012; 55(6):2005–23.

8. Abd El-Kader SM, El-Den Ashmawy EM. Non-alcoholic fatty liver disease: The diagnosis and management. World J Hepatol. 2015; 7(6):846–58. [PubMed: 25937862]

9. Lazo M, Clark JM. The epidemiology of nonalcoholic fatty liver disease: a global perspective. Semin Liver Dis. 2008; 28(4):339–50. [PubMed: 18956290]

*10. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology (Baltimore, Md). 2016; 64(1):73–84. This meta-analysis provided the distribution of NAFLD worldwide, raising questions as to whether the variation in NAFLD prevalence in the would mirror the variation in NAFLD among individuals with HIV around the world, supporting a hypothesis of a genetic predisposition to NAFLD in individuals with HIV.

11. Foster T, Anania FA, Li D, Katz R, Budoff M. The prevalence and clinical correlates of nonalcoholic fatty liver disease (NAFLD) in African Americans: the multiethnic study of atherosclerosis (MESA). Dig Dis Sci. 2013; 58(8):2392–8. [PubMed: 23546700]

12. Williams CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology. 2011; 140(1):124–31. [PubMed: 20858492]

13. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology (Baltimore, Md). 2004; 40(6):1387–95.

14. Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology. 2015; 148(3):547–55. [PubMed: 25461851]

15. Cholankeril, G., Nadelson, J., Ahmed, A., Satapathy, S., Nair, S. NASH Liver Transplantation Within the Elderly: Age-specific Cohort Differences in Transplant Trends and Outcomes in NASH, HCV and ALD. American College of Gastroenterology Annual Scientific Meeting; Oct. 14–19, 2016; Las Vegas, NV. 2016.

16. Younossi ZM, Stepanova M, Negro F, Hallaji S, Younossi Y, Lam B, et al. Nonalcoholic fatty liver disease in lean individuals in the United States. Medicine (Baltimore). 2012; 91(6):319–27. [PubMed: 23117851]

17. Newton JL. Systemic symptoms in non-alcoholic fatty liver disease. Dig Dis. 2010; 28(1):214–9. [PubMed: 20460914]

18. Loomba R, Cui J, Wolfson T, Haufe W, Hooker J, Szeverenyi N, et al. Novel 3D Magnetic Resonance Elastography for the Noninvasive Diagnosis of Advanced Fibrosis in NAFLD: A Prospective Study. The American journal of gastroenterology. 2016; 111(7):986–94. [PubMed: 27002798]

19. Dulai PS, Sirlin CB, Loomba R. MRI and MRE for non-invasive quantitative assessment of hepatic steatosis and fibrosis in NAFLD and NASH: Clinical trials to clinical practice. J Hepatol. 2016; 65(5):1006–16. [PubMed: 27312947]

20. Doycheva I, Cui J, Nguyen P, Costa EA, Hooker J, Hofflich H, et al. Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE. Aliment Pharmacol Ther. 2016; 43(1):83–95. [PubMed: 26369383]

21. Verhaegh P, Bavalia R, Winkens B, Masclee A, Jonkers D, Koek G. Non-invasive diagnosis for differentiating non-alcoholic steatohepatitis from simple steatosis: a meta-analysis and systematic review. Clin Gastroenterol Hepatol. 2017

22. Kotronen A, Peltonen M, Hakkarainen A, Sevastianova K, Bergholm R, Johansson LM, et al. Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors. Gastroenterology. 2009; 137(3):865–72. [PubMed: 19524579]

23. Seeff LB, Everson GT, Morgan TR, Curto TM, Lee WM, Ghany MG, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. Clin Gastroenterol Hepatol. 2010; 8(10):877–83. [PubMed: 20362695]

24. Boyum JH, Atwell TD, Schmit GD, Poterucha JJ, Schleck CD, Harmsen WS, et al. Incidence and Risk Factors for Adverse Events Related to Image-Guided Liver Biopsy. Mayo Clin Proc. 2016; 91(3):329–35. [PubMed: 26837481]

25. Ratziu V, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology. 2005; 128(7):1898–906. [PubMed: 15940625]
26. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. Gastroenterology. 2015; 149(2):367–78e5. quiz e14–5. [PubMed: 25865049]
27. Ryan MC, Itsiopoulos C, Thodis T, Ward G, Trost N, Hofferberth S, et al. The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease. J Hepatol. 2013; 59(1):138–43. [PubMed: 23485520]
28. Caldwell S. NASH Therapy: omega 3 supplementation, vitamin E, insulin sensitizers and statin drugs. Clinical and molecular hepatology. 2017; 23(2):103–8. [PubMed: 28494529]
29. Lavine JE, Schwimmer JB, Van Natta ML, Molleston JP, Murray KF, Rosenthal P, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. JAMA. 2011; 305(16):1659–68. [PubMed: 21521847]
30. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010; 362(18):1675–85. [PubMed: 20427778]
31. Bugianesi E, Gentilcore E, Manini R, Natale S, Vanni E, Villanova N, et al. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. The American journal of gastroenterology. 2005; 100(5):1082–90. [PubMed: 15842582]
*32. 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 (Baltimore, Md). 2017 This paper provides the latest clinical guidance for and challenges in diagnosis and management of NAFLD.
33. Klein EA, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 2011; 306(14):1549–56. [PubMed: 21990298]
34. Schurks M, Glynn RJ, Rist PM, Tzourio C, Kurth T. Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials. BMJ. 2010; 341:c5702. [PubMed: 21051774]
35. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med. 2005; 142(1):37–46. [PubMed: 15537682]
36. Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, et al. Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized Trial. Ann Intern Med. 2016; 165(5):305–15. [PubMed: 27322798]
37. Yau H, Rivera K, Lomonaco R, Cusi K. The future of thiazolidinedione therapy in the management of type 2 diabetes mellitus. Curr Diab Rep. 2013; 13(3):329–41. [PubMed: 23625197]
38. Liao HW, Saver JL, Wu YL, Chen TH, Lee M, Ovbiagele B. Pioglitazone and cardiovascular outcomes in patients with insulin resistance, pre-diabetes and type 2 diabetes: a systematic review and meta-analysis. BMJ Open. 2017; 7(1):e013927.
39. Lewis JD, Habel LA, Quesenberry CP, Strom BL, Peng T, Hedderson MM, et al. Pioglitazone Use and Risk of Bladder Cancer and Other Common Cancers in Persons With Diabetes. JAMA. 2015; 314(3):265–77. [PubMed: 26197187]
40. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet. 2015; 385(9972):956–65. [PubMed: 25468160]
41. Stanley TL, Feldpausch MN, Oh J, Branch KL, Lee H, Torriani M, et al. Effect of tesamorelin on visceral fat and liver fat in HIV-infected patients with abdominal fat accumulation: a randomized clinical trial. JAMA. 2014; 312(4):380–9. [PubMed: 25038357]

42. 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 (Baltimore, Md). 2017

43. Scorletti E, Bhatia L, McCormick KG, Clough GF, Nash K, Hodson L, et al. Effects of purified eicosapentaenoic and docosahexaenoic acids in nonalcoholic fatty liver disease: results from the Welcome* study. Hepatology (Baltimore, Md). 2014; 60(4):1211–21.

44. Ratziu V, Harrison SA, Francque S, Bedossa P, Lehert P, Serfaty L, et al. Elafibranor, an Agonist of the Peroxisome Proliferator-Activated Receptor-alpha and -delta, Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening. Gastroenterology. 2016; 150(5):1147–59e5. [PubMed: 26874076]

45. Trickey A, May MT, Vehreschild J, Obel N, Gill MJ, Crane H, et al. Cause-Specific Mortality in HIV-Positive Patients Who Survived Ten Years after Starting Antiretroviral Therapy. PLoS One. 2016; 11(8):e0160460. [PubMed: 27525413]

46. Domingues CS, Waldman EA. Causes of death among people living with AIDS in the pre- and post-HAART Eras in the city of Sao Paulo, Brazil. PLoS One. 2014; 9(12):e114661. [PubMed: 25500837]

47. Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. Lancet. 2014; 384(9939):241–8. [PubMed: 25042234]

48. De Socio GV, Pucci G, Baldelli F, Schillaci G. Observed versus predicted cardiovascular events and all-cause death in HIV infection: a longitudinal cohort study. BMC Infect Dis. 2017; 17(1): 414. [PubMed: 28606059]

49. Rafiq N, Stepanova M, Lam B, Nader F, Srishord M, Younossi ZM. Predictors of chronic liver disease in individuals with human immunodeficiency virus infection. Ann Hepatol. 2013; 13(1): 60–4. [PubMed: 24378267]

*50. 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(3):365–73. One of the few studies that include women with HIV to compare steatosis between individuals with and without HIV. When adjusted for VAT, women without HIV had 34% more fatty liver than women with HIV. [PubMed: 27831949]

51. 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. The American journal of gastroenterology. 2014; 109(5):695–704. [PubMed: 24642579]

52. Nishijima T, Gatanaga H, Shimbo T, Komatsu H, Nozaki Y, Nagata N, et al. Traditional but not HIV-related factors are associated with nonalcoholic fatty liver disease in Asian patients with HIV-1 infection. PLoS One. 2014; 9(1):e87596. [PubMed: 24498148]

53. Scheiner B, Mandorfer M, Schwabl P, Payer BA, Bucsics T, Bota S, et al. The Impact of PNPLA3 rs738409 SNP on Liver Fibrosis Progression, Portal Hypertension and Hepatic Steatosis in HIV/HCV Coinfection. PLoS One. 2015; 10(11):e0143429. [PubMed: 26599080]

54. Morse CG, McLaughlin M, Matthews L, Proschan M, Thomas F, Gharib AM, et al. Nonalcoholic Steatohepatitis and Hepatic Fibrosis in HIV-1-Monoinfected Adults With Elevated Aminotransferase Levels on Antiretroviral Therapy. Clin Infect Dis. 2015; 60(10):1569–78. [PubMed: 25681381]

55. Jimenez-Sousa MA, Berenguer J, Garcia-Alvarez M, Gutierrez-Rivas M, Aldamiz-Echevarria T, Tejerina F, et al. Impact of patatin-like phospholipase domain-containing 3 gene polymorphism (rs738409) on severity of liver disease in HIV/hepatitis C virus-coinfected patients. Aids. 2016; 30(3):465–70. [PubMed: 26760234]

56. 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(5):464–73. [PubMed: 19225402]

57. 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(2):250–7. [PubMed: 18532884]

58. Lui G, Wong VS, Wong GH, Chu WW, Wong CK, Yung I, et al. Liver fibrosis and fatty liver in Asian HIV-infected patients. Alimentary pharmacology & therapeutics. 2016; 44(4):411–21. [PubMed: 27301337]

*59. Macias J, Rivero-Juarez A, Neukam K, Tellez F, Merino D, Frias M, et al. Impact of genetic polymorphisms associated with nonalcoholic fatty liver disease on HIV-infected individuals. Aids. 2015; 29(15):1927–35. Although the role of PNPLA3 gene is NAFLD is well established in individuals without HIV, this study shows that PNPLA3 is not independently associated with NAFLD in individuals with HIV. Instead, polymorphism in SAMM50 gene is associated with fatty liver disease. [PubMed: 26352879]

60. Vodkin I, Valasek MA, Bettencourt R, Cachay E, Loomba R. Clinical, biochemical and histological differences between HIV-associated NAFLD and primary NAFLD: a case-control study. Aliment Pharmacol Ther. 2015; 41(4):368–78. [PubMed: 25496369]

61. 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. Journal of acquired immune deficiency syndromes (1999). 2007; 45(4):432–8. [PubMed: 17558337]

62. Study of Fat R, Metabolic Change in HIVI. Fat distribution in women with HIV infection. Journal of acquired immune deficiency syndromes (1999). 2006; 42(5):562–71. [PubMed: 16837863]

63. Brown TT, Xu X, John M, Singh J, Kingsley LA, Palella FJ, et al. Fat distribution and longitudinal anthropometric changes in HIV-infected men with and without clinical evidence of lipodystrophy and HIV-uninfected controls: a substudy of the Multicenter AIDS Cohort Study. AIDS Res Ther. 2009; 6:8. [PubMed: 19439092]

64. Joy T, Keogh HM, Hadigan C, Dolan SE, Fitch K, Liebau J, et al. Relation of body composition to body mass index in HIV-infected patients with metabolic abnormalities. J Acquir Immune Defic Syndr. 2008; 47(2):174–84. [PubMed: 17971710]

65. Perez-Matute P, Perez-Martinez L, Blanco JR, Oteo JA. Role of mitochondria in HIV infection and associated metabolic disorders: focus on nonalcoholic fatty liver disease and lipodystrophy syndrome. Oxid Med Cell Longev. 2013; 2013:493413. [PubMed: 23970949]

66. Cote HC. Possible ways nucleoside analogues can affect mitochondrial DNA content and gene expression during HIV therapy. Antivir Ther. 2005; 10(Suppl 2):M3–11. [PubMed: 16152702]

67. Mallon PW. Antiretroviral therapy-induced lipid alterations: in-vitro, animal and human studies. Curr Opin HIV AIDS. 2007; 2(4):282–92. [PubMed: 19372900]

68. Payne BA, Wilson IJ, Hateley CA, Horvath R, Santibanez-Koref M, Samuels DC, et al. Mitochondrial aging is accelerated by anti-retroviral therapy through the clonal expansion of mtDNA mutations. Nature genetics. 2011; 43(8):806–10. [PubMed: 21706004]

69. Macias J, Mancebo M, Merino D, Tellez F, Montes-Ramirez ML, Pulido F, et al. Changes in Liver Steatosis After Switching From Efavirenz to Raltegravir Among Human Immunodeficiency Virus-Infected Patients With Nonalcoholic Fatty Liver Disease. Clin Infect Dis. 2017; 65(6):1012–9. [PubMed: 28903510]

70. Agarwal N, Iyer D, Gabbi C, Saha P, Patel SG, Mo Q, et al. HIV-1 viral protein R (Vpr) induces fatty liver in mice via LXRalpha and PPARalpha dysregulation: implications for HIV-specific pathogenesis of NAFLD. Sci Rep. 2017; 7(1):13362. [PubMed: 29042644]

71. Mave V, Erlandson KM, Gupte N, Balagopal A, Asmuth DM, Campbell TB, et al. Inflammation and Change in Body Weight With Antiretroviral Therapy Initiation in a Multinational Cohort of HIV-Infected Adults. J Infect Dis. 2016; 214(1):65–72. [PubMed: 26962236]

72. 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 journal of gastroenterology. 2014; 20(48):18070–91. [PubMed: 25561778]

73. 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(1):87–97. [PubMed: 20680289]

74. Athyros VG, Alexandrides TK, Bilianou H, Cholongitas E, Doumas M, Ganotakis ES, et al. The use of statins alone, or in combination with pioglitazone and other drugs, for the treatment of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and related cardiovascular risk. An

Expert Panel Statement. Metabolism: clinical and experimental. 2017; 71:17–32. [PubMed: 28521870]

75. El Kamari, V., Hileman, C., McComsey, G. Fatty liver disease in HIV: Predictors and response to statin therapy (Abstract #1813). San Diego, CA: ID Week; 10/7/02017
76. Dinh DM, Volpe GE, Duffalo C, Bhalchandra S, Tai AK, Kane AV, et al. Intestinal microbiota, microbial translocation, and systemic inflammation in chronic HIV infection. J Infect Dis. 2015; 211(1):19–27. [PubMed: 25057045]
77. Compare D, Coccoli P, Rocco A, Nardone OM, De Maria S, Carteni M, et al. Gut--liver axis: the impact of gut microbiota on non alcoholic fatty liver disease. Nutr Metab Cardiovasc Dis. 2012; 22(6):471–6. [PubMed: 22546554]
78. Henao-Mejia J, Elinav E, Jin C, Hao L, Mehal WZ, Strowig T, et al. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature. 2012; 482(7384):179–85. [PubMed: 22297845]
79. Perez-Matute P, Perez-Martinez L, Aguilera-Lizarraga J, Blanco JR, Oteo JA. Maraviroc modifies gut microbiota composition in a mouse model of obesity: a plausible therapeutic option to prevent metabolic disorders in HIV-infected patients. Revista espanola de quimioterapia: publicacion oficial de la Sociedad Espanola de Quimioterapia. 2015; 28(4):200–6. [PubMed: 26200028]
80. Komazaki R, Katagiri S, Takahashi H, Maekawa S, Shiba T, Takeuchi Y, et al. Periodontal pathogenic bacteria, Aggregatibacter actinomycetemcomitans affect non-alcoholic fatty liver disease by altering gut microbiota and glucose metabolism. Sci Rep. 2017; 7(1):13950. [PubMed: 29066788]
81. Woodhouse CA, Patel VC, Singanayagam A, Shawcross DL. Review article: the gut microbiome as a therapeutic target in the pathogenesis and treatment of chronic liver disease. Aliment Pharmacol Ther. 2017
82. Rich NE, Oji S, Mufti AR, Browning JD, Parikh ND, Odewole M, et al. Racial and Ethnic Disparities in Non-alcoholic Fatty Liver Disease Prevalence, Severity, and Outcomes in the United States: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2017
83. Kallwitz ER, Guzman G, TenCate V, Vitello J, Layden-Almer J, Berkes J, et al. The histologic spectrum of liver disease in African-American, non-Hispanic white, and Hispanic obesity surgery patients. The American journal of gastroenterology. 2009; 104(1):64–9. [PubMed: 19098851]
84. Lomonaco R, Ortiz-Lopez C, Orsak B, Finch J, Webb A, Bril F, et al. Role of ethnicity in overweight and obese patients with nonalcoholic steatohepatitis. Hepatology (Baltimore, Md). 2011; 54(3):837–45.
85. Sookoian S, Pirola CJ. Genetic predisposition in nonalcoholic fatty liver disease. Clinical and molecular hepatology. 2017; 23(1):1–12. [PubMed: 28268262]
86. Pan JJ, Fallon MB. Gender and racial differences in nonalcoholic fatty liver disease. World J Hepatol. 2014; 6(5):274–83. [PubMed: 24868321]
87. Medrano LM, Jimenez-Sousa MA, Fernandez-Rodriguez A, Resino S. Genetic Polymorphisms Associated with Liver Disease Progression in HIV/HCV-Coinfected Patients. AIDS Rev. 2017; 19(1):3–15. [PubMed: 28182609]
88. Sookoian S, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. Hepatology (Baltimore, Md). 2011; 53(6):1883–94.
89. Sookoian S, Castano GO, Burgueno AL, Gianotti TF, Rosselli MS, Pirola CJ. A nonsynonymous gene variant in the adiponutrin gene is associated with nonalcoholic fatty liver disease severity. J Lipid Res. 2009; 50(10):2111–6. [PubMed: 19738004]
90. Speliotes EK, Yerges-Armstrong LM, Wu J, Hernaez R, Kim LJ, Palmer CD, et al. Genome-wide association analysis identifies variants associated with nonalcoholic fatty liver disease that have distinct effects on metabolic traits. PLoS genetics. 2011; 7(3):e1001324. [PubMed: 21423719]
91. Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nature genetics. 2008; 40(12): 1461–5. [PubMed: 18820647]

92. Honda Y, Yoneda M, Kessoku T, Ogawa Y, Tomeno W, Imajo K, et al. Characteristics of non-obese non-alcoholic fatty liver disease: Effect of genetic and environmental factors. Hepatol Res. 2016; 46(10):1011–8. [PubMed: 26763865]

93. Sagnelli C, Merli M, Uberti-Foppa C, Hasson H, Cirillo G, Grandone A, et al. Impact of PNPLA3 variants on liver histology of 168 patients with HIV infection and chronic hepatitis C. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2016; 22(4):372–8.

94. Dold L, Luda C, Schwarze-Zander C, Boesecke C, Hansel C, Nischalke HD, et al. Genetic polymorphisms associated with fatty liver disease and fibrosis in HIV positive patients receiving combined antiretroviral therapy (cART). PLoS One. 2017; 12(6):e0178685. [PubMed: 28594920]

95. National Center for Biotechnology Information. PLPPR4 phospholipid phosphatase related 4 [Homo sapiens (human)]. 2017. [Available from: https://www.ncbi.nlm.nih.gov/gene/9890

96. Garcia-Alvarez M, Guzman-Fulgencio M, Berenguer J, Micheloud D, Campos Y, Lopez JC, et al. European mitochondrial DNA haplogroups and liver fibrosis in HIV and hepatitis C virus coinfected patients. AIDS. 2011; 25(13):1619–926. [PubMed: 21673559]

97. Ballestri S, Nascimbeni F, Baldelli E, Marrazzo A, Romagnoli D, Lonardo A. NAFLD as a Sexual Dimorphic Disease: Role of Gender and Reproductive Status in the Development and Progression of Nonalcoholic Fatty Liver Disease and Inherent Cardiovascular Risk. Adv Ther. 2017; 34(6): 1291–326. [PubMed: 28526997]

98. Graff M, North KE, Franceschini N, Reiner AP, Feitosa M, Carr JJ, et al. PNPLA3 gene-by-visceral adipose tissue volume interaction and the pathogenesis of fatty liver disease: the NHLBI family heart study. International journal of obesity (2005). 2013; 37(3):432–8. [PubMed: 22546774]

99. Ayonrinde OT, Olynyk JK, Beilin LJ, Mori TA, Pennell CE, de Klerk N, et al. Gender-specific differences in adipose distribution and adipocytokines influence adolescent nonalcoholic fatty liver disease. Hepatology (Baltimore, Md). 2011; 53(3):800–9.

100. Brady CW. Liver disease in menopause. World journal of gastroenterology. 2015; 21(25):7613–20. [PubMed: 26167064]

101. Huang Y, He S, Li JZ, Seo YK, Osborne TF, Cohen JC, et al. A feed-forward loop amplifies nutritional regulation of PNPLA3. Proc Natl Acad Sci U S A. 2010; 107(17):7892–7. [PubMed: 20385813]

102. D'Eon TM, Souza SC, Aronovitz M, Obin MS, Fried SK, Greenberg AS. Estrogen regulation of adiposity and fuel partitioning. Evidence of genomic and non-genomic regulation of lipogenic and oxidative pathways. J Biol Chem. 2005; 280(43):35983–91. [PubMed: 16109719]

103. Ingiliz P, Valantin MA, Duvivier C, Medja F, Dominguez S, Charlotte F, et al. Liver damage underlying unexplained transaminase elevation in human immunodeficiency virus-1 mono-infected patients on antiretroviral therapy. Hepatology (Baltimore, Md). 2009; 49(2):436–42.

104. Vuille-Lessard E, Lebouche B, Lennox L, Routy JP, Costiniuk CT, Pexos C, et al. Nonalcoholic fatty liver disease diagnosed by transient elastography with controlled attenuation parameter in unselected HIV monoinfected patients. AIDS. 2016; 30(17):2635–43. [PubMed: 27603289]

*105. Remigio-Baker RA, Allison MA, Forbang NI, Loomba R, Anderson CAM, Budoff M, et al. Race/ethnic and sex disparities in the non-alcoholic fatty liver disease-abdominal aortic calcification association: The Multi-Ethnic Study of Atherosclerosis. Atherosclerosis. 2017; 258:89–96. By showing that Blacks with NAFLD have higher likelihood of aortic calcification than whites, this paper suggests that the variation in genetic predisposition could be accompanied by the fact that progression of NAFLD and its related metabolic disease may differ by race and ethnicity. [PubMed: 28235711]

106. Du T, Sun X, Yuan G, Zhou X, Lu H, Lin X, et al. Sex differences in the impact of nonalcoholic fatty liver disease on cardiovascular risk factors. Nutr Metab Cardiovasc Dis. 2017; 27(1):63–9. [PubMed: 27956025]

107. Giltay EJ, Elbers JM, Gooren LJ, Emeis JJ, Kooistra T, Asscheman H, et al. Visceral fat accumulation is an important determinant of PAI-1 levels in young, nonobese men and women: modulation by cross-sex hormone administration. Arterioscler Thromb Vasc Biol. 1998; 18(11): 1716–22. [PubMed: 9812909]

108. Giltay EJ, Gooren LJ, Emeis JJ, Kooistra T, Stehouwer CD. Oral ethinyl estradiol, but not transdermal 17beta-estradiol, increases plasma C-reactive protein levels in men. Thromb Haemost. 2000; 84(2):359–60. [PubMed: 10959719]

109. Elbers JM, Giltay EJ, Teerlink T, Scheffer PG, Asscheman H, Seidell JC, et al. Effects of sex steroids on components of the insulin resistance syndrome in transsexual subjects. Clin Endocrinol (Oxf). 2003; 58(5):562–71. [PubMed: 12699437]

110. Wilson R, Spiers A, Ewan J, Johnson P, Jenkins C, Carr S. Effects of high dose oestrogen therapy on circulating inflammatory markers. Maturitas. 2009; 62(3):281–6. [PubMed: 19231116]

Table 1

Prevalence of NAFLD and its risk factors in studies of patients with HIV.

Reference	n	Age*	M:F	BMI	Race, Nationality, or Ethnicity	Method of Diagnosis	Genotype (%)	NAFLD (%)	Identified Risk Factors	Factors that did not significantly contribute
Rafiq et al., 2013(49)	14,685: 79 HIV+ 14,606 HIV−	HIV+: 38 HIV− 35	3:1, HIV+ 1:1 HIV−	n/a	HIV+: 31% White; 52% Black HIV−: 67% White, 12% Black	Men: ALT>40, AST>37 Women: ALT/AST >31	Unknown	HIV+ 19.3 HIV− 10.9	HIV	
Kardashian et al., 2017(50)	228: 121 HIV+ 107 HIV−	35–70	3:2	n/a	US: (race/ethnicity n/a)	Liver Fat Fraction Measured on Magnetic Resonance Imaging and Spectroscopy	Unknown	**Women:** HIV+ 1.9 HIV− 3.1 **Men:** HIV+ 4.6 HIV− 4.1	high VAT, insulin resistance (HIV+)	CD4+ cell count, HIV RNA level, ART
Price et al., 2014(51)	719: 465 HIV+ 254 HIV−	53	100:0	25.8	56% White	Liver-spleen attenuation values of <1.1 on Non-contrast Computed Tomography	**PNPL A3**-60 CC 35 GC 4.4 GG	HIV+ 13 HIV− 19	**VAT, insulin resistance,** PNPLA3 non-CC genotype (in HIV+), dideoxynucle oside analogs (in HIV+)	GCKR (rs780094), LYPLAL1 (rs12137855) and PPP1R3b (rs4240624) HIV-PNPLA3 (rs738409)
Nishijima et al., 2014 (52)	435 HIV+	>17	n/a	n/a	Japan	Abdominal Ultrasound	Unknown	31	BMI, dyslipidemia, higher ALT:AST ratio	Dideoxynucle oside analogues, duration of ART
Scheiner et al., 2015(53)	177 HIV/HCV	39	3:1	23.1	Austria (race/ethnicity n/a)	Liver biopsy, Transient Elastography with Controlled Attenuation Parameter	**PNPL A3**-57.8 CC: 37.3 GC: 5.1 GG: **IL28B**-10.2 TT: 57.1 TC: 32.2 CC	n/a	HCV-GT3, BMI, age	PNPLA3, L28B-genotype
Morse et al., 2015(54)	62 HIV+	n/a	n/a	n/a	US: (race/ethnicity n/a)	Liver Biopsy	Unknown	55 (NASH)	PNPLA3 minor allele, insulin resistance, obesity	Duration of HIV or ART, specific ART, history of OI, immune status, or duration of AST/ALT elevation
Jimenez - Sousa et al., 2016(55)	215 HIV/HCV	n/a	n/a	n/a	Spain	Liver Biopsy	**PNPL A3**-0.05 CC: 0.38 GC: 0.57G G	**NAFLD** CC: 70 CG: 64 GG: 57 **Fibrosis >3** CC: 0 CG: 19 GG:: 25	n/a	n/a
Crum-Cianflone et al., 2009(56)	216 HIV	40+/−11	9:1	26	48% White, 27% Black, 14% Hispanic, 11% other	Liver Biopsy	Unknown	White: 35 African Americans: 31	BMI, waist circumference, lower HDL levels, higher triglyceride levels, use	CD4 cell count, HIV-1 RNA, duration of HIV infection and ART

Reference	n	Age*	M:F	BMI	Race, Nationality, or Ethnicity	Method of Diagnosis	Genotype (%)	NAFLD (%)	Identified Risk Factors	Factors that did not significantly contribute
									of lipid- lowering medication, metabolic syndrome	
Guaraldi et al., 2008(57)	225 HIV	48	3:1	23.2	Italian	Liver-spleen attenuation values of <1.1 on Non-contrast Computed Tomography	Unknown	Infected: 37	Higher ALT:AST ratio male sex, greater waist circumference, longer NRTI exposure	Coronary artery calcium scores, diabetes
Lui et al., 2016(58)	240: 80 HIV+ 160 HIV−	54+/−11	9:1	n/a	Chinese	Transient Elastography and Proton Magnetic Resonance Spectroscopy	Unknown	HIV+: 28.7 HIV−: 27.5	n/a	n/a
Macias et al., 2015(59)	431: 275 HIV/HCV 156 HIV+	42–50	4:1	23.3	Spain	Transient Elastography	Unknown	NAFLD: 41.5 NASH: 28.3 **SAMM50**: TT: 60.5 CT/CC: 39.6 **rs12743824**: AC/AA: 37.8 CC: 49.2	Dominant SAMM50 rs738491-T allele	dominant LPPR4 rs12743824-A allele

*Mean, median, or range; n/a= not available

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; VAT, visceral adipose tissue; BMI, body mass index; NRTI, nucleotide reverse transcriptase inhibitor; ART, antiretroviral therapy; OI, opportunistic infection; AST, aspartate aminotransferase; ALT, alanine aminotransferase

Table 2

Role of PNPLA3 in NAFLD in Adults without HIV, with HIV, and with HIV/Hepatitis C Virus Co-infection

	HIV-uninfected	HIV-infected	HIV/Hepatitis C Virus Co-infected
Positive associations	**Speliotes et al., 2011**(88): PNPLA3 is associated with NAFLD	**Price et al., 2014**(51): PNPLA3 non-CC genotype (rs738409) is independently associated with increased odds of fatty liver (OR=3.30; 95 % CI=1.66, 6.57; p=0.001) **Morse et al., 2015**(54): G allele is 3.9 times more likely to be present in NASH than non-specific changes on liver biopsy.	**Jimenez-Sousa et al., 2016**(55): PNPLA3 minor allele is associated with NASH (CC: 0% CG: 18.5% GG: 25.2%; p=.029)
Negative associations	**Price et al., 2014** (51): PNPLA3 (rs738409) is not significantly associated with fatty liver (OR=1.14; 95 % CI=0.51, 2.54; P=0.75).		**Schreiner et al., 2015**(53): PNPLA3 allele is not an independent risk factor for NAFLD **Jimenez-Sousa et al., 2016**(55): PNPLA3 minor allele is not associated with NAFLD (CC: 70% CG: 63.4% GG: 57.9%; p=0.26)

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis