Contents available at **PubMed**
www.aidsreviews.com

PERMANYER

AIDS Rev. 2017;19:190-7

Non-Alcoholic Fatty Liver Disease and HIV/AIDS: A New Way of Modulation of Cardiovascular Risk

Mohamed H. Ahmed[1], Nazik Elmalaika Husain[2], Akif Malik[3], Clare Woodward[4] and Dushyant Mital[4]

[1]Department of Medicine and HIV Metabolic Clinic, Milton Keynes University Hospital NHS Foundation Trust, Eaglestone, Milton Keynes, Buckinghamshire, UK; [2]Department of Pathology, Faculty of Medicine and Health Sciences, Omdurman Islamic University, Khartoum, Sudan; [3]Department of Medicine and [4]Department of HIV and Genitourinary Medicine; Milton Keynes University Hospital, NHS Foundation Trust, Milton Keynes, UK

Abstract

With the advent and subsequent success of antiretroviral therapy, HIV infection has largely become a chronic condition and is increasingly seen alongside metabolic disorders such as dyslipidemia and insulin resistance. Furthermore, the administration of antiretroviral therapy itself is associated with an increase in the incidence of metabolic risk factors, namely insulin resistance, lipoatrophy, dyslipidemia, and abnormalities of fat distribution, in HIV patients. Thus, further challenges in the management of HIV patients include the management of diabetes and the metabolic syndrome, non-alcoholic fatty liver disease. Importantly, HIV and non-alcoholic fatty liver disease are both associated with increased risk of cardiovascular disease. Overall, the management of non-alcoholic fatty liver disease and cardiovascular risks associated with HIV is complex and requires specialist management. Further research is needed to address the best strategies in the management of cardiovascular disease in patients with HIV. This narrative review aims to discuss non-alcoholic fatty liver disease and HIV infection, HIV and cardiovascular disease, as well as how fatty liver modulates cardiovascular disease in HIV patients. **(AIDS Rev. 2015;17:190-7)**

Corresponding author: Mohamed H. Ahmed, elziber@yahoo.com

Key words

HIV. Fatty liver. Insulin resistance. Cardiovascular disease.

Introduction

HIV infection is a widespread, but well-controlled, disease that has seen a rise in metabolic problems as patients increasingly have life expectancies comparable to those without the infection[1]. The administration of a combination of antiretroviral therapy (cART) is associated with an increase in the incidence of certain metabolic risk factors (insulin resistance, lipoatrophy, dyslipidemia, and abnormalities of fat distribution) in HIV patients[2,3]. Furthermore, HIV infection itself is associated with insulin resistance and dyslipidemia (high triglycerides, low high-density lipoprotein [HDL] and both low cholesterol and low-density lipoprotein-c [LDL-c]). Possible mechanisms to explain this include increased cytokines level (tumor necrosis factor and interleukin-6), decreased lipid clearance, and increased hepatic synthesis of the very low-density lipoprotein[1-3]. Therefore, HIV is regarded as an independent risk factor for cardiovascular disease (CVD)[4,5].

The presence of insulin resistance, dyslipidemia, and lipoatrophy are all precursor factors that lead to the

Correspondence to:
Mohamed H. Ahmed
Department of Medicine and HIV Metabolic Clinic
Milton Keynes University Hospital NHS Foundation Trust
Eaglestone, Milton Keynes
Buckinghamshire, UK
E-mail: elziber@yahoo.com

development of non-alcoholic fatty liver disease (NAFLD). The estimated prevalence of NAFLD in populations without HIV is thought to be around 25-35% across the globe[6]. NAFLD refers to a wide spectrum of liver damage, rating from simple steatosis to steatohepatitis, advanced fibrosis, and cirrhosis. Importantly, NAFLD has gained significant attention since it is increasing in prevalence across the globe with an increase in both mortality and morbidity[7]. The association of NAFLD with insulin resistance, obesity, and type 2 diabetes is well established in the literature[8-12]. For instance, the prevalence of NAFLD within type 2 diabetics can range between 42-62%[13-17]. NAFLD is associated with high risk of CVD and mortality, especially in the presence of liver fibrosis[17-19]. Besides the fact that diabetes and obesity run risk elements for hepatocellular carcinoma (HCC), NAFLD is also regarded as risk factor for HCC and among the top three leading causes of liver disease among adults awaiting liver transplantation in the USA since 2009[20-27]. HIV per se can induce all this spectrum of liver diseases[28]. These include viral hepatitis, hepatotoxicity (drug-associated), and NAFLD (drug-associated and unassociated). In addition to the well-known effect of alcohol on the liver and risk of systemic infections and malignancies, hepatitis (A, B, C, D, E) are important risk factors in HIV patients. Anti-retroviral drugs can be related to liver toxicity and risk of metabolic syndrome and NAFLD[24-29]. Importantly, baseline analysis of the INSIGHT Strategic Timing of Anti-Retroviral Treatment (START) trial showed that significant liver fibrosis was observed in approximately 8% of participants[29].

Thus, the presence of NAFLD in patients with HIV should warrant further screening for advanced liver disease, diabetes, and cardiovascular risk factors. This narrative review aims to discuss NAFLD and HIV infection, HIV and CVD, as well as how fatty liver modulates CVD in HIV patients.

Non-alcoholic fatty liver disease and HIV infection

The prevalence of NAFLD among HIV patients varies from 13% in the USA to 31% in Asian countries[30,31]. Interestingly, it is present in HIV-infected persons with lower body mass indices (BMI) and more physically active compared with HIV-negative patients[32]. It is prevalent among different ethnic populations, with particularly higher incidence and a more aggressive course in Hispanics[33].

NAFLD is increasingly being diagnosed in patients with nonspecific symptoms with an incidental elevation of aminotransferases[34]. In a case-control study in HIV-infected patients with biopsy-proven NAFLD, patients with HIV-associated NAFLD had significantly higher mean aspartate aminotransferase (AST; $p < 0.001$), alanine aminotransferase (ALT; $p < 0.001$), alkaline phosphatase ($p = 0.003$) and serum triglycerides ($p = 0.024$) than controls. Furthermore, this study also showed that patients with HIV-associated NAFLD had significantly higher rates of definite steatohepatitis, and more features of liver injury, including lobular inflammation (< 0.001) and acidophil bodies (< 0.001). The authors concluded that HIV-associated NAFLD is associated with an increased severity of liver disease as well as a higher prevalence of nonalcoholic steatohepatitis[28].

Those HIV-infected adults with chronic aminotransferase elevations while receiving antiretroviral therapy (ART) have a high rate of liver disease, which is a leading cause of non-AIDS-related mortality in persons infected with HIV[35]. There are an estimated 40 million HIV-infected individuals worldwide, with chronic liver disease being the second leading cause of mortality in this population. Abnormal liver functions are usually observed in HIV patients, and the etiologies are varied. Viral hepatitis B (HBV) and C (HCV) fatty liver as well as drug-induced liver injury are predominant[28]. HBV and HCV co-infection were found to be associated with liver-related deaths in HIV individuals[36]. Spradling, et al. found that NAFLD or alcohol consumption was attributed to enzyme elevations in HBV infection[37]. This further emphasizes the contribution of NAFLD in the causation of liver disease in HIV individuals.

In the Multicenter AIDS Cohort Study (MACS), interestingly, although HIV infection was associated with a lower prevalence of fatty liver compared to unaffected individuals (odds ratio [OR]: 0.44; $p = 0.002$), a higher prevalence of fatty liver was seen in participants with patatin-like phospholipase domain containing 3 (PNPLA3, rs738409) non-CC genotype (OR: 2.06; $p = 0.005$), increased abdominal visceral adipose tissue (OR: 1.08 per 10 cm^2; $p < 0.001$), and homeostatic model assessment of insulin resistance (HOMA-IR) ≥ 4.9 (OR: 2.50; $p = 0.001$). Moreover, among HIV-infected men, PNPLA3 (rs738409) non-CC genotype was found to be linked to a more prominent prevalence of fatty liver (OR: 3.30; $p = 0.001$) and cumulative dideoxynucleoside exposure (OR: 1.44 per five years; $p = 0.02$). The MACS investigators concluded that

fatty liver is common among men at risk for HIV infection and is related to higher visceral adiposity, HOMA-IR, and PNPLA3 (rs738409)[31]. Furthermore, LPPR4 and SAMM50 allelic variants have been identified as independent risk factors for simple steatosis and steatohepatitis development, respectively, in HIV-infected individuals[38].

On the other hand, Nishijima, et al. demonstrated that NAFLD was associated with a high BMI, dyslipidemia, and high ALT/AST ratio, but not with HIV-related factors among Asian patients with HIV-1 infection. This was first suggested by Mohammed, et al. in 2007[32]. It is worth mentioning that their studied patients were free of chronic HBV or HCV infection and without excessive alcohol intake. Their results highlighted the great value of early identification and management of NAFLD and traditional factors associated with NAFLD[30].

There is some suggestion in the literature that antiretroviral treatment for HIV is associated with NAFLD[38]. For example, Price, et al. showed, in a multicenter study, that CT-defined NAFLD is common among men at risk of HIV infection and is linked to larger visceral adiposity and insulin resistance, and prolonged exposure to dideoxynucleoside analogues is associated with higher prevalence of NAFLD[31].

Diabetes mellitus, metabolic syndrome, and HIV

Several studies have shown that NAFLD is strongly associated with diabetes, metabolic syndrome, and dyslipidemia. Diabetes mellitus (DM) prevalence estimates in patients with HIV are reported as being as high as 14%[39]. The relationship between DM and HIV is complex and not well understood. In the Data Collection of Adverse Events of Anti-HIV Drugs (D:A:D) study, Smith, et al. investigated emerging trends in causes of death amongst HIV-positive individuals and investigated the factors associated with each specific cause of death[36]. They identified AIDS (n = 743; rate/1,000 person years = 4.12), liver-related (341; 1.89), CVD-related (289; 1.60), and non-AIDS malignancy (286; 1.59) as primary causes of death in HIV cART-treated patients. Interestingly, diabetes was a risk factor for all specific causes of death except non-AIDS cancers. Furthermore, there is some suggestion in the literature that HIV infection is an independent risk factor for the development of DM[39,40]. However, this is controversial as other studies do not support this notion[41,42].

Dyslipidemia and increased blood glucose are the most common metabolic abnormalities seen among HIV patients on ART worldwide. Menezes de Padua, et al., in their cohort study, obtained information on long-term adverse drug reactions to ART from the medical records of treatment-naive HIV-infected adult patients initiating ART[43]. Out of 233 records studied, dyslipidemia was found in 19.3% and diabetes in 2.1%. An increase in the prevalence of lipoatrophy, insulin resistance, and diabetes, particularly with ART, has been demonstrated in a number of studies[41,44]. Preclinical studies support the idea that ART may induce diabetes since protease inhibitors have been shown to increase insulin resistance through effects on the glucose transporter type 4 (GLUT-4) receptor[45]. The clinical relevance of this, however, is unknown. Having said this, there is strong association with certain first-generation ART agents, e.g. stavudine and indinavir, and DM as one cohort study has evidenced that the peaks and troughs regarding the use of these agents correlate directly with the peaks and troughs of the incidence of DM in HIV patients over a 10-year period[46]. Furthermore, Ledergerber, et al. suggested that current treatment with protease inhibitor- and nucleoside reverse transcriptase inhibitor-containing regimens specifically was associated with the risk of developing type 2 DM[47].

The risk of dyslipidemia significantly rises with accumulative exposure to ART. Tripathi, et al. found that there is a significantly higher risk of dyslipidemia in the ART-treated HIV-infected group (adjusted hazard ratio [aHR]: 1.18; 95% CI: 1.07-1.30) and a significantly lower risk in the cART-naive HIV-infected group (aHR: 0.66; 95% CI: 0.53-0.82) compared to the control non-HIV-infected group[48]. They also found that pre-existing hypertension, obesity, and diabetes increased the risk of dyslipidemia, whereas HCV, depressed CD4(+) T-cell count, and higher HIV viral load had a protective effect.

Statins are used for managing hypercholesterolemia and CVD in both HIV and non-HIV patients alike. The association between diabetes and statin treatment has been ascertained by various studies[52-54]. It is debatable whether the risk of incidental diabetes related to the administration of statins fosters HIV and ART-associated risk of insulin resistance. Nevertheless, continuously monitoring plasma glucose in HIV patients on statin therapy is a recommended clinical practice. More studies are needed to assess whether statin administration in individuals with HIV conveys an increased risk for diabetes. Otherwise, the likely cardiovascular event reduction benefits from taking statins likely outweigh the risk of increased insulin resistance[49,50].

Fasting plasma glucose is routinely used in the diagnosis of DM. Furthermore, HbA1C is used as a measure of glycated hemoglobin and reflects long-term glucose control. However, in patients with HIV, there is growing evidence to suggest that the use of HbA1C may be an underestimation of their glycemic status[51-55]. Monroe, et al. argue that fasting plasma glucose should be used for the diagnosis of DM in HIV patients, especially in light of HbA1C inaccuracies[56]. Current recommendations are that fasting plasma glucose should be measured every 6-12 months in patients with HIV and should be considered 1-3 months after the commencement of ART[56].

Overall, HIV is a chronic inflammatory condition, which may lead to insulin resistance. Alongside certain antiretroviral medications, associated dyslipidemia and changes in body conformation (central obesity, truncal obesity, lipoatrophy) hasten the process that leads to DM in the context of HIV infection.

HIV and cardiovascular disease

People living with HIV infection are at increased risk of CVD compared to patients without CVD (relative risk [RR]: 1.61 for people not on ART; 95% CI: 1.43-1.83; and RR: 2.00 for people on ART; 95% CI: 1.70-2.37)[57]. Major cardiovascular-related risk factors are prevalent among patients with HIV. The prevalence rate of hypertension, dyslipidemia, and diabetes has been reported to be 26, 48, and 13%, respectively, in such patients[58]. Furthermore, in a healthcare, system-based cohort study, Triant, et al. found that among HIV patients, higher prevalence of smoking (38 vs. 18%), hypertension (21 vs. 16%), diabetes (12 vs. 7%), and dyslipidemia (23 vs. 18%) were found compared to non-HIV patients[59]. Interestingly, some small studies exist indicating a possible increase in the number of ST-elevation myocardial infarctions versus non-ST-elevation myocardial infarctions in patients with HIV[60].

The D:A:D study is a large database incorporating 33,308 patients with HIV, studied over 10 years[36]. In this study, they demonstrated 289 of the 2,482 deaths were accounted for by CVD. They found that in patients with HIV, at baseline, smoking rates were high (76%), 76% were male, 22% had total cholesterol ≥ 6.2 mmol/l, 34% had triglycerides ≥ 2.3 mmol/l, and 26% had an HDL-cholesterol ≤ 0.9 mmol/l. Furthermore, at baseline, only a few had hypertension (8.5%) and DM (2.5%).

There is some evidence that certain antiretroviral drugs may raise the risk of cardiovascular disease. Bavinger, et al. produced an observational data meta-analysis demonstrating that increased risk of myocardial infarction is seen in patients exposed to abacavir (RR: 1.92; 95% CI: 1.51-2.42) and protease inhibitors (RR: 2.13; 95% CI: 1.06-4.28), and an increased risk associated with each additional year of exposure to indinavir (RR: 1.11; 95% CI: 1.05-1.17) and lopinavir (RR: 1.22; 95% CI: 1.01-1.47)[61]. Hemken, et al. cautioned that the studies put into these meta-analyses were of mixed quality and heterogeneous, and therefore should be interpreted with care[62]. Furthermore, Cruciani, et al. re-analyzed in a meta-analysis all randomized control trials comparing abacavir with reverse-transcriptase inhibitor controls, finding no increased risk of myocardial infarctions with abacavir exposure (RR: 0.73; 95% CI: 0.39-1.35)[63]. Increasing evidence suggests that HIV suppression is associated with a decreased risk of CVD[62]. Thus, early initiation of ART should be balanced with the potential detrimental effects of ART with regards to CVD, amid other comorbidities. Part of the issue is that the full spectrum of side effects of ART is not entirely known. Thus, further research is required to elucidate this delicate balance. The START (Strategic Timing of AntiRetroviral Treatment) study is a randomized, controlled clinical trial designed to determine whether taking ART immediately would lead to a lower risk of AIDS and serious events, and the trial was expected to end in December 2016[64]. Interestingly, in the subgroup analysis, CVD risk factors are common among START participants; at least one in every two participants had one or more CVD risk factors. Therefore, it is expected that the final analysis may reveal CVD as the main component of the primary end point[65].

Interestingly, dyslipidemia is also increasingly being recognized in HIV-infected children[66]. The HIV-infected children may be at risk of premature CVD as it has been demonstrated that they have high levels of total and non-HDL cholesterol and triglycerides[67]. Furthermore, it has been postulated that HIV-infected adolescents are amenable to aggregated atherosclerotic CVD risk[68]. Interestingly, coronary heart disease was reported in only 2.15% of 3,760 HIV-infected patients in a Mediterranean cohort study, raising the question of how significant the impact of HIV is on CVD or the importance of genetic factors[69]. The D:A:D study demonstrated that the rate of a congestive heart disease (CHD) episode was 7.52 times higher in those with pre-existing CHD than in those without preexisting CHD, but it was only 2.41 times higher in those with preexisting DM compared with those without DM[75]. Protease inhibitors are also known to significantly increase the risk of CHD in HIV patients[76].

Table 1. Summary of some studies demonstrating an association between non-alcoholic fatty liver disease and cardiovascular disease

Study reference	Cardiovascular impact	Main outcome
[70, 71]	A. Coronary artery disease	Increase cardiac calcification
[72]		NAFLD is associated with higher prevalence of IMT
[73]		NAFLD is associated with high prevalence of atherosclerosis in the absence of diabetes and metabolic syndrome
[74]		Histologically proven NAFLD independently predicts IMT
[75, 76]	B. Endothelial dysfunction	NAFLD is associated with endothelial dysfunction
[77, 78]		NAFLD is associated with arterial stiffness
[79, 80]	C. Risk of clotting	NAFLD is associated with increased thrombotic risk factors
[81, 82]	D. High inflammatory markers	NAFLD is associated with high inflammatory marker
[83, 84]	E. Structural heart changes	NAFLD is associated with pathological changes in cardiac structure and function
[85, 86]	F. Liver enzymes and CVD	High GGT and ALT are associated with CVD

ALT: alanine transaminase; CVD: cardiovascular disease; GGT: gamma-glutamyl transferase; IMT: intima-media thickness; NAFLD: non-alcoholic fatty liver disease.

In the view of the fact that NAFLD may also be associated with CVD and the unique nature of the relationship between HIV and CVD, this may lead to the question whether the presence of NAFLD may also modulate CVD in HIV patients?

Does non-alcoholic fatty liver disease modulate cardiovascular disease in HIV patients?

Several studies have shown the association of NAFLD with CVD, as presented in table 1. The increased risk of CVD in NAFLD is partially due to dyslipidemia, DM, renal disease, chronic inflammation, and presence of ectopic fat. NAFLD is also shown to be associated with independent risk of CVD. HIV is a chronic inflammation associated with high risk of CVD and this can also be mediated in part by dyslipidemia, DM, renal disease, and the presence of metabolic syndrome. It is tempting to conclude that the presence of NAFLD can also be associated with high risk of CVD (Fig. 1). Importantly, further research is needed to establish how NAFLD can modulate the risk of CVD in HIV patients.

Non-alcoholic fatty liver disease treatment and whether it can modulate cardiovascular disease

Treatment of NAFLD targeted an array of disease mechanisms like insulin resistance, obesity, dyslipidemia, inflammation, lipotoxic liver injury, and liver fibrosis. Medications that have potential benefit in treating NAFLD are metformin, pioglitazone, incretin, statins, sodium-glucose co-transporter 2 inhibitors, and antioxidants like vitamin E. A summary of the effect of these medications on NAFLD and CVD can be found in table 2[87,88]. However, a recent meta-analysis concluded that it is difficult to conclude with certainty about the effectiveness of pharmacological therapy for NAFLD[89]. Therefore, lifestyle changes in term of weight loss, increased physical activity, and decreased carbohydrate intake can be recommended until scientific evidence or treatment can be found. It is possible to conclude that treatment of NAFLD in individuals living with HIV likely will be the same as the general population[90]. It is worth mentioning that further clinical trials are needed to explore specifically whether treatment of NAFLD may modulate CVD risk in individuals living with HIV (Table 2).

Conclusion

HIV is a metabolic condition associated with dyslipidemia, diabetes, metabolic syndrome and CVD. These metabolic changes can be due to the HIV per se or due to the antiretroviral treatment. Importantly, NAFLD is also associated with insulin resistance, dyslipidemia, diabetes, and CVD. Therefore, the presence of fatty liver in HIV patients may also add the risk of CVD (Fig. 1). Further research is needed to establish the role of

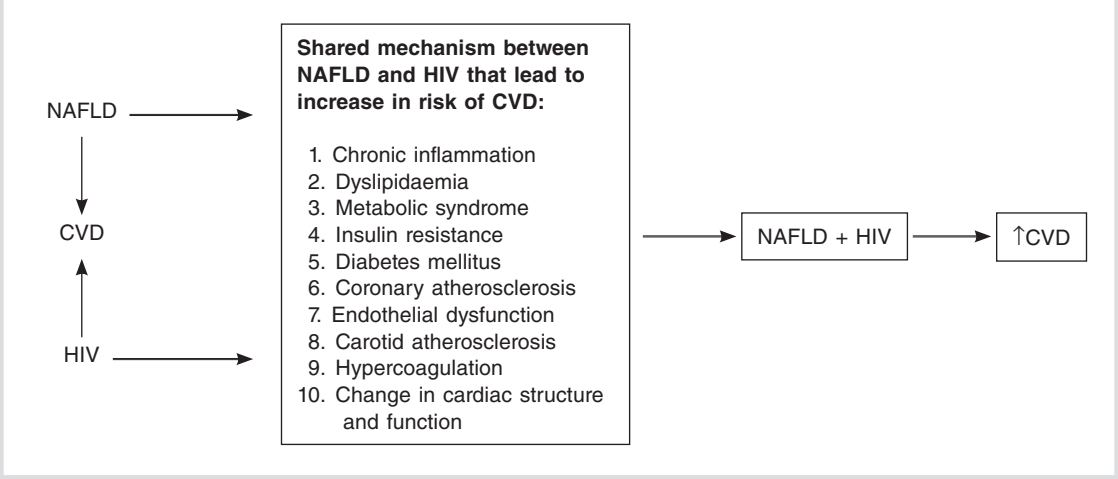

Figure 1. *Illustration showing a possible summary of interaction between HIV and non-alcoholic fatty liver disease in the modulation of cardiovascular risk factors and how this can lead to increase the risk of cardiovascular disease in HIV patients with non-alcoholic fatty liver disease. CVD: cardiovascular disease; NAFLD: non-alcoholic fatty liver disease.*

Table 2. Summary of treatment of non-alcoholic fatty liver disease and whether such treatment may modulate cardiovascular disease

Medication	NAFLD	CVD	References
Metformin	– Inhibition of hepatic gluconeogenesis and lipogenesis increased glucose uptake in the muscle and increased fatty acid oxidation in the liver and adipose tissue – Clinical studies show improvement in liver enzymes but not histology	Decrease in CVD	[91-94]
Pioglitazone	– Promote and maintain the whole body insulin sensitivity – Clinical studies show improvement in liver enzymes and inflammation and potential improvement in liver histology	Decrease in CVD	[95-98]
GLP-1 analogues (liraglutide)	– GLP-1 promotes weight loss, enhances insulin resistance and prevents hepatic fat accumulation – Clinical studies show improvement in liver enzymes and inflammation but not consistent improvement histology	Decrease in CVD	[99-103]
DPP-4 inhibitors (Sitagliptin)	– Inhibits fatty liver, inflammation and improves insulin sensitivity – Clinical studies show improvement in fatty liver inflammation with degree of improvement in liver histology	Decrease in CVD	[103-108]
Statins	– Rosuvastatin and atorvastatin decrease hyperlipidemia and fatty liver; further benefit seen in combination with dietary control and ezetimibe – Clinical studies show improvement in fatty liver Meta-analysis confirmed the benefit but not liver histology	Decrease in CVD	[109-112]
Antioxidants (Vitamin E, silymarin, betaine, pentoxifylline)	– Potential benefit shown in treatment of NAFLD	NO benefit in decreasing CVD risk	[89, 95] [113]
Weight loss (orlistat, bariatric surgery and dietary restriction)	– Orlistat, bariatric surgery and dietary restriction all associated with radiological and histological improvement of fatty liver	Decrease in CVD	[114, 115] [8]

CVD: cardiovascular disease; GLP-1: glucagon-like peptide-1; NAFLD: non-alcoholic fatty liver disease.

NAFLD in the modulation of CVD in HIV patients. Therefore, metabolic and cardiovascular risk factors will need to be managed in a specialized clinic.

Declaration of interest

The authors state no conflict of interest and have received no payment in the preparation of this manuscript.

References

1. Lewden C, et al. All-cause mortality in treated HIV-infected adults with CD4 >/=500/mm3 compared with the general population: evidence from a large European observational cohort collaboration. Int J Epidemiol. 2012;41:433-45.
2. Mothe B, et al. HIV-1 infection in subjects older than 70: a multicenter cross-sectional assessment in Catalonia, Spain. Curr HIV Res. 2009;7:597-600.
3. Hejazi N, et al. Metabolic abnormalities in adult HIV infected population on antiretroviral medication in Malaysia: a cross-sectional survey. BMC Public Health. 2013;13:758.
4. Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. N Engl J Med. 2005;352:48-62.
5. Worm SW, et al. Diabetes mellitus, preexisting coronary heart disease, and the risk of subsequent coronary heart disease events in patients infected with human immunodeficiency virus: The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D Study). Circulation. 2009;119:805-11.
6. Ahmed MH, Barakat S, Almobarak AO. Nonalcoholic fatty liver disease and cardiovascular disease: has the time come for cardiologists to be hepatologists? J Obes. 2012;2012:483135.
7. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol. 2013;10:330-44.
8. Hafeez S, Ahmed MH. Bariatric surgery as potential treatment for nonalcoholic fatty liver disease: a future treatment by choice or by chance? J Obes. 2013;2013:839275.
9. Kim HJ, et al. Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. Arch Intern Med. 2004;164:2169-75.
10. Adams LA, et al. Nonalcoholic fatty liver disease increases risk of death among patients with diabetes: a community-based cohort study. Am J Gastroenterol. 2010;105:1567-73.
11. Bedogni G, et al. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. Hepatology. 2005;42:44-52.
12. Browning JD, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology. 2004;40:1387-95.
13. Williamson RM, et al. Prevalence of and risk factors for hepatic steatosis and nonalcoholic Fatty liver disease in people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetes Care. 2011;34:1139-44.
14. Targher G, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care. 2007;30:1212-8.
15. Chan WK, et al. Non-alcoholic fatty liver disease in diabetics--prevalence and predictive factors in a multiracial hospital clinic population in Malaysia. J Gastroenterol Hepatol. 2013;28:1375-83.
16. Lv WS, et al. Nonalcoholic fatty liver disease and microvascular complications in type 2 diabetes. World J Gastroenterol. 2013;19:3134-42.
17. Ferreira VS, et al. Frequency and risk factors associated with non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus. Arq Bras Endocrinol Metabol. 2010;54:362-8.
18. Ekstedt M, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology. 2015;61:1547-54.
19. Brunt EM. Nonalcoholic steatohepatitis. Semin Liver Dis. 2004;24:3-20.
20. de Marco R, et al. Cause-specific mortality in type 2 diabetes. The Verona Diabetes Study. Diabetes Care. 1999;22:756-61.
21. Konfortion J, et al. Time and deprivation trends in incidence of primary liver cancer subtypes in England. J Eval Clin Pract. 2014;20:498-504.
22. Ladep NG, et al. Incidence and mortality of primary liver cancer in England and Wales: changing patterns and ethnic variations. World J Gastroenterol. 2014;20:1544-53.
23. Stickel F, Hellerbrand C. Non-alcoholic fatty liver disease as a risk factor for hepatocellular carcinoma: mechanisms and implications. Gut. 2010;59:1303-7.
24. Wong RJ, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology. 2015;148:547-55.
25. Charlton MR, et al. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. Gastroenterology. 2011;141:1249-53.
26. Agopian VG, et al. Liver transplantation for nonalcoholic steatohepatitis: the new epidemic. Ann Surg. 2012;256:624-33.
27. Burra P, Germani G. Orthotopic liver transplantation in non-alcoholic fatty liver disease patients. Rev Recent Clin Trials. 2014;9:210-6.
28. Acharya C, Dharel N, Sterling RK. Chronic liver disease in the human immunodeficiency virus patient. Clin Liver Dis. 2015;19:1-22.
29. Matthews GV, et al. Baseline prevalence and predictors of liver fibrosis among HIV-positive individuals: a substudy of the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Med. 2015;16(Suppl 1):129-36.
30. Nishijima T, et al. Traditional but not HIV-related factors are associated with nonalcoholic fatty liver disease in Asian patients with HIV-1 infection. PLoS One. 2014;9:e87596.
31. Price JC, et al. Risk factors for fatty liver in the Multicenter AIDS Cohort Study. Am J Gastroenterol. 2014;109:695-704.
32. Mohammed SS, 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. J Acquir Immune Defic Syndr. 2007;45:432-8.
33. Debes JD, et al. Fatty Liver in Hispanics with HIV. AIDS Res Hum Retroviruses. 2016;32:515-6.
34. Younossi ZM, Henry L. Economic and quality-of-life implications of nonalcoholic fatty liver disease. Pharmacoeconomics. 2015;33:1245-53.
35. Morse CG, et al. Nonalcoholic steatohepatitis and hepatic fibrosis in HIV-1-monoinfected adults with elevated aminotransferase levels on antiretroviral therapy. Clin Infect Dis. 2015;60:1569-78.
36. Data Collection on Adverse Events of Anti-HIV drugs (D:A:D) Study Group; Smith C, Sabin CA, Lundgren JD, et al. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study. AIDS. 2010;24:1537-48.
37. Spradling PR, et al. Prevalence and causes of elevated serum aminotransferase levels in a population-based cohort of persons with chronic hepatitis B virus infection. J Hepatol. 2014;61:785-91.
38. Macias J, et al. Impact of genetic polymorphisms associated with nonalcoholic fatty liver disease on HIV-infected individuals. AIDS. 2015;29:1927-35.
39. Brown TT, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. Arch Intern Med. 2005;165:1179-84.
40. Galli L, et al. Risk of type 2 diabetes among HIV-infected and healthy subjects in Italy. Eur J Epidemiol. 2012;27:657-65.
41. Rasmussen LD, et al. Risk of diabetes mellitus in persons with and without HIV: a Danish nationwide population-based cohort study. PLoS One. 2012;7:e44575.
42. Butt AA, et al. HIV infection and the risk of diabetes mellitus. AIDS. 2009;23:1227-34.
43. Menezes de Padua CA, Moura CS. Availability of data on adverse reactions to antiretroviral drugs in medical charts according to the naranjo algorithm: an example of a Brazilian historical cohort. Clin Drug Investig. 2014;34:395-402.
44. Tungsiripat M, et al. Rosiglitazone improves lipoatrophy in patients receiving thymidine-sparing regimens. AIDS. 2010;24:1291-8.
45. Hruz PW. Molecular mechanisms for insulin resistance in treated HIV-infection. Best Pract Res Clin Endocrinol Metab. 2011;25:459-68.
46. Capeau J, et al. Ten-year diabetes incidence in 1046 HIV-infected patients started on a combination antiretroviral treatment. AIDS. 2012;26:303-14.
47. Ledergerber B, et al. Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV Cohort Study. Clin Infect Dis. 2007;45:111-9.
48. Tripathi A, et al. Association of clinical and therapeutic factors with incident dyslipidemia in a cohort of human immunodeficiency virus-infected and non-infected adults: 1994-2011. Metab Syndr Relat Disord. 2013;11:417-26.
49. Wang KL, et al. Statins, risk of diabetes, and implications on outcomes in the general population. J Am Coll Cardiol. 2012;60:1231-8.
50. Ridker PM, et al. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention. Lancet. 2012;380:565-71.
51. Kim PS, et al. A1C underestimates glycemia in HIV infection. Diabetes Care. 2009;32:1591-3.
52. Diop ME, et al. Inappropriately low glycated hemoglobin values and hemolysis in HIV-infected patients. AIDS Res Hum Retroviruses. 2006;22:1242-7.
53. Polgreen PM, Putz D, Stapleton JT. Inaccurate glycosylated hemoglobin A1C measurements in human immunodeficiency virus-positive patients with diabetes mellitus. Clin Infect Dis. 2003;37:e53-6.
54. Glesby MJ, et al. Glycated haemoglobin in diabetic women with and without HIV infection: data from the Women's Interagency HIV Study. Antivir Ther. 2010;15:571-7.
55. Slama L, et al. Inaccuracy of haemoglobin A1c among HIV-infected men: effects of CD4 cell count, antiretroviral therapies and haematological parameters. J Antimicrob Chemother. 2014;69:3360-7.

56. Monroe AK, Glesby MJ, Brown TT. Diagnosing and managing diabetes in HIV-infected patients: current concepts. Clin Infect Dis. 2015;60: 453-62.
57. Islam FM, et al. Relative risk of cardiovascular disease among people living with HIV: a systematic review and meta-analysis. HIV Med. 2012;13:453-68.
58. Chu C, et al. Comorbidity-related treatment outcomes among HIV-infected adults in the Bronx, NY. J Urban Health. 2011;88:507-16.
59. Triant VA, et al. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab. 2007;92:2506-12.
60. Boccara F, et al. HIV and coronary heart disease: time for a better understanding. J Am Coll Cardiol. 2013;61:511-23.
61. Bavinger C, et al. Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review. PLoS One. 2013;8:e59551.
62. Hemkens LG, Bucher HC. HIV infection and cardiovascular disease. Eur Heart J. 2014;35:1373-81.
63. Cruciani M, et al. Abacavir use and cardiovascular disease events: a meta-analysis of published and unpublished data. AIDS. 2011;25:1993-2004.
64. Cerrato E, et al. Cardiovascular disease in HIV patients: from bench to bedside and backwards. Open Heart. 2015;2:e000174.
65. Baker JV, et al. Assessment of arterial elasticity among HIV-positive participants with high CD4 cell counts: a substudy of the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Med. 2015;16(Suppl 1):109-18.
66. Kamin D, Hadigan C. Hyperlipidemia in children with HIV infection: an emerging problem. Expert Rev Cardiovasc Ther. 2003;1:143-50.
67. Miller TI, et al. Metabolic abnormalities and viral replication are associated with biomarkers of vascular dysfunction in HIV-infected children. HIV Med. 2012;13:264-75.
68. Patel K, et al. Aggregate risk of cardiovascular disease among adolescents perinatally infected with the human immunodeficiency virus. Circulation. 2014;129:1204-12.
69. Echeverria P, et al. Prevalence of ischemic heart disease and management of coronary risk in daily clinical practice: results from a Mediterranean cohort of HIV-infected patients. Biomed Res Int. 2014;2014:823058.
70. Chen CH, et al. Association between nonalcoholic fatty liver disease and coronary artery calcification. Dig Dis Sci. 2010;55:1752-60.
71. Kim D, et al. Nonalcoholic fatty liver disease is associated with coronary artery calcification. Hepatology. 2012;56:605-13.
72. Lankarani KB, et al. Common carotid intima-media thickness in patients with non-alcoholic fatty liver disease: a population-based case-control study. Korean J Gastroenterol. 2013;62:344-51.
73. Kang JH, et al. Relationship between nonalcoholic fatty liver disease and carotid artery atherosclerosis beyond metabolic disorders in non-diabetic patients. J Cardiovasc Ultrasound. 2012;20:126-33.
74. Targher G, et al. Relations between carotid artery wall thickness and liver histology in subjects with nonalcoholic fatty liver disease. Diabetes Care. 2006;29:1325-30.
75. Sesti G, et al. Association between noninvasive fibrosis markers and cardio-vascular organ damage among adults with hepatic steatosis. PLoS One. 2014;9:e104941.
76. Tarantino G, et al. Carotid intima-media thickness is predicted by combined eotaxin levels and severity of hepatic steatosis at ultrasonography in obese patients with nonalcoholic fatty liver disease. PLoS One. 2014;9:e105610.
77. Sunbul M, et al. Arterial stiffness in patients with non-alcoholic fatty liver disease is related to fibrosis stage and epicardial adipose tissue thickness. Atherosclerosis. 2014;237:490-3.
78. Tripodi A, et al. Procoagulant imbalance in patients with non-alcoholic fatty liver disease. J Hepatol. 2014;61:148-54.
79. Cao X, et al. Association between sleep condition and arterial stiffness in Chinese adult with nonalcoholic fatty liver disease. J Thromb Thrombolysis. 2016;42:127-34.
80. Foroughi M, et al. Relationship between non-alcoholic fatty liver disease and inflammation in patients with non-alcoholic fatty liver. Adv Biomed Res. 2016;5:28.
81. Riquelme A, et al. Non-alcoholic fatty liver disease and its association with obesity, insulin resistance and increased serum levels of C-reactive protein in Hispanics. Liver Int. 2009;29:82-8.
82. Petta S, et al. Epicardial fat, cardiac geometry and cardiac function in patients with non-alcoholic fatty liver disease: association with the severity of liver disease. J Hepatol. 2015;62:928-33.
83. Mantovani A, et al. Non-alcoholic fatty liver disease is independently associated with left ventricular hypertrophy in hypertensive Type 2 diabetic individuals. J Endocrinol Invest. 2012;35:215-8.
84. Jousilahti P, Rastenyte D, Tuomilehto j. Serum gamma-glutamyl transferase, self-reported alcohol drinking, and the risk of stroke. Stroke. 2000; 31:1851-5.
85. Wannamethee G, Ebrahim S, Shaper AG. Gamma-glutamyltransferase: determinants and association with mortality from ischemic heart disease and all causes. Am J Epidemiol. 1995;142:699-708.
86. Yeung EN, et al. Fibrinogen production is enhanced in an in-vitro model of non-alcoholic fatty liver disease: an isolated risk factor for cardiovascular events? Lipids Health Dis. 2015;14:86.
87. Neuschwander-Tetri BA. Non-alcoholic fatty liver disease. BMC Med. 2017;15:45.
88. Mazzotti A, et al. Which treatment for type 2 diabetes associated with non-alcoholic fatty liver disease? Dig Liver Dis. 2017;49:235-40.
89. Lombardi R, et al. Pharmacological interventions for non-alcohol related fatty liver disease (NAFLD): an attempted network meta-analysis. Cochrane Database Syst Rev. 2017;3:CD011640.
90. Macias J, Pineda JA, Real LM. Non-alcoholic fatty liver disease in HIV infection. AIDS Rev. 2017;19:35-46.
91. Kita Y, et al. Metformin prevents and reverses inflammation in a non-diabetic mouse model of nonalcoholic steatohepatitis. PLoS One. 2012;7:e43056.
92. Bugianesi E, et al. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. Am J Gastroenterol. 2005;100:1082-90.
93. Uygun A, et al. Metformin in the treatment of patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2004;19:537-44.
94. Garinis GA, et al. Metformin versus dietary treatment in nonalcoholic hepatic steatosis: a randomized study. Int J Obes (Lond). 2010;34: 1255-64.
95. Belfort R, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med. 2006;355:2297-307.
96. Sanyal AJ, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010;362:1675-85.
97. Aithal GP, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. Gastroenterology. 2008;135:1176-84.
98. Boettcher E, et al. Meta-analysis: pioglitazone improves liver histology and fibrosis in patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2012;35:66-75.
99. Trevaskis JL, et al. Glucagon-like peptide-1 receptor agonism improves metabolic, biochemical, and histopathological indices of nonalcoholic steatohepatitis in mice. Am J Physiol Gastrointest Liver Physiol. 2012; 302:G762-72.
100. Armstrong MJ, et al. Safety and efficacy of liraglutide in patients with type 2 diabetes and elevated liver enzymes: individual patient data meta-analysis of the LEAD program. Aliment Pharmacol Ther. 2013; 37:234-42.
101. Klonoff DC, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. Curr Med Res Opin. 2008;24:275-86.
102. Kenny PR, et al. Exenatide in the treatment of diabetic patients with non-alcoholic steatohepatitis: a case series. Am J Gastroenterol. 2010;105:2707-9.
103. Kern M, et al. Linagliptin improves insulin sensitivity and hepatic steatosis in diet-induced obesity. PLoS One. 2012;7:e38744.
104. Klein T, et al. Linagliptin alleviates hepatic steatosis and inflammation in a mouse model of non-alcoholic steatohepatitis. Med Mol Morphol. 2014;47:137-49.
105. Shirakawa J, et al. Diet-induced adipose tissue inflammation and liver steatosis are prevented by DPP-4 inhibition in diabetic mice. Diabetes. 2011;60:1246-57.
106. Iwasaki T, et al. Sitagliptin as a novel treatment agent for non-alcoholic Fatty liver disease patients with type 2 diabetes mellitus. Hepatogastroenterology. 2011;58:2103-5.
107. Yilmaz Y, et al. Effects of sitagliptin in diabetic patients with nonalcoholic steatohepatitis. Acta Gastroenterol Belg. 2012;75:240-4.
108. Balaban YH, et al. Dipeptidyl peptidase IV (DDP IV) in NASH patients. Ann Hepatol. 2007;6:242-50.
109. Foster T, et al. Atorvastatin and antioxidants for the treatment of nonalcoholic fatty liver disease: the St Francis Heart Study randomized clinical trial. Am J Gastroenterol. 2011;106:71-7.
110. Nakahara T, et al. Efficacy of rosuvastatin for the treatment of non-alcoholic steatohepatitis with dyslipidemia: An open-label, pilot study. Hepatol Res. 2012;42:1065-72.
111. Nelson A, et al. A pilot study using simvastatin in the treatment of nonalcoholic steatohepatitis: A randomized placebo-controlled trial. J Clin Gastroenterol. 2009;43:990-4.
112. Gomez-Dominguez E, et al. A pilot study of atorvastatin treatment in dyslipemid, non-alcoholic fatty liver patients. Aliment Pharmacol Ther. 2006;23:1643-7.
113. Zeng T, et al. Pentoxifylline for the treatment of nonalcoholic fatty liver disease: a meta-analysis of randomized double-blind, placebo-controlled studies. Eur J Gastroenterol Hepatol. 2014;26:646-53.
114. Promrat K, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology. 2010;51:121-9.
115. Lazo M, et al. Effect of a 12-month intensive lifestyle intervention on hepatic steatosis in adults with type 2 diabetes. Diabetes Care. 2010;33: 2156-63.