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New drugs for non-alcoholic steatohepatitis and HIV infection: great expectations with a great absent?

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ABSTRACT

In recent years, there has been an increasing number of clinical trials for the treatment of non-alcoholic steatohepatitis (NASH). People living with HIV (PLWH) are commonly excluded from these studies, usually due to concerns over drug-drug interactions (DDI) associated with antiretroviral therapy (ART). The Steatohepatitis in HIV Emerging Research (SHIVER) Network, a group of international experts in hepatology and infectious diseases, discusses our current understanding on the interaction between HIV and NASH, and the issues related to the inclusion of PLWH in NASH clinical trials. Recent trials addressing NASH treatment in PLWH are discussed. The risk of DDI between ART and aramchol, cenicriviroc, elafibranor, obeticholic acid and resmetirom (MGL-3196), which are currently in phase III trials for the treatment of NASH, are reviewed. Finally, a model for trial design to include PLWH is proposed, strongly advocating for the scientific community to include this group as a sub-population within studies.

Introduction

The Steatohepatitis in HIV Emerging Research (SHIVER) Network, a group of international experts in hepatology and infectious diseases, convened recently for a conference focused on non-alcoholic fatty liver disease (NAFLD) in people living with HIV (PLWH) [1]. NAFLD is defined as fat accumulation in >5% hepatocytes without a secondary cause such as alcohol consumption and can be evaluated with non-invasive diagnostic tools, such as ultrasound, transient elastography, computed tomography and magnetic resonance imaging. Non-alcoholic steatohepatitis (NASH) is a histological diagnosis defined by liver steatosis with hepatocyte ballooning and lobular inflammation, leading to progressive hepatocellular injury [2]. NASH affects 3-7% of the general population [2] and without interventions can progress to advanced liver fibrosis, cirrhosis and related end-stage liver complications namely ascites, hepatic encephalopathy, variceal bleeding, hepatocellular carcinoma and hepatic failure. In the general population, the disease burden is increasing so fast that currently NASH represents the second most common indication for liver transplantation in North America, with projections to become the leading indication over the next 10 years [3]. NASH is already the leading indication for liver transplantation in women [4].

As PLWH live longer due to effective early treatment with antiretroviral therapy (ART), chronic non-infectious co-morbidities (NICM) are an increasingly important aspect of the medical care in this aging population. As a result, there is interest in how chronic HIV infection and long-term drug treatment may affect the trajectory of aging-related conditions, such as liver and cardiovascular disease. Liver disease is a leading cause of non-AIDS related deaths in PLWH [5]. While in the past co-infections with hepatitis C (HCV) and B (HBV) viruses have driven this trend, NAFLD/NASH has become the most frequent liver disease in PLWH [6].

Available data paint a fairly equivocal picture on the role of HIV and associated drug exposure on the development and progression of NAFLD/NASH in PLWH. But there is also an increasing number of studies suggesting that metabolic disorders play a key role in the development of NAFLD/NASH as observed in non-HIV patients [7–9].

The purpose of this review is to discuss the current understanding on the interaction between HIV and NASH, and the issues related to the inclusion of PLWH in NASH clinical trials.

We reviewed in detail the risk of drug-drug interactions (DDI) between ART and NAFLD/NASH agents which are currently in phase III trials and we suggest a model for trial design to include PLWH, strongly advocating for the scientific community to include this group as a sub-population within studies.

The link between non-alcoholic steatohepatitis, HIV and ART

The prevalence of NAFLD in HIV mono-infection is about 35% [7], higher than the global average of 23-25% [10,11], but highly variable depending on different geographical areas and diagnostic tools. Table 1 summarizes the prevalence of NAFLD and NASH in PLWH, lists associated risk factors and specifies diagnostic procedures used to define this condition. It should be noted that well matched studies are lacking, and there is no conclusive evidence about a different prevalence of NAFLD in PLWH in comparison to the general population.

The first NAFLD phenotype related to either HIV or HCV infection, occasionally defined as 'virus-associated fatty liver disease', was characterized by a lean constitution, associated with insulin resistance (particularly characteristic of HCV-genotype 3 infection) or central fat redistribution in HIV (central fat accumulation with facial and limb lipodystrophy). In this setting, pathogenetic mechanisms have been identified including chronic immune-activation, gut dysbiosis, oxidative stress and mitochondrial toxicities [12,13], (Figure 1). In the general population, the prevalence of lean NAFLD ranges between 7% in the United States to 19% in Asia [14] with cohort studies suggesting it might be higher in PLWH [15,16].

More recently, in the changing scenario of HIV clinical presentation and management, the current clinical phenotype of NAFLD closely resembles patients in the general population. In this setting, the metabolic complications of obesity are overwhelmingly associated with the disease. Importantly, this is also the case in the progressive forms of the disease with NASH and fibrosis, which are most consistently associated with features of the metabolic syndrome rather than HIV-specific factors such as drug exposure or CD4 nadir [7].

This immuno-metabolic phenomenon is often described as "inflammaging" [17], and is pathogenically linked with metabolic syndrome [18], NICM [19], functional decline [20] and geriatric syndromes [21]. In this context, both NAFLD and HIV infection are multisystemic

diseases affecting multiple organs, being associated with increased risk of age-related NICMs including, among others, type 2 diabetes mellitus, cardiovascular disease, and chronic kidney disease. In PLWH, NAFLD does not merely represent a risk factor, but it is also involved in pathogenesis of NICMs [22], suggesting NAFLD as a barometer of metabolic aging.

ART-induced hepatotoxicity and significant metabolic complications exist [12]. However, these side effects were mainly attributed to D-drugs - didanosine and stavudine- which have been phased out in the last decade due to induced mitochondrial functional impairment [23], (Figure 1).

A recent pre-clinical model has shown a putative mechanism linking efavirenz to the development of steatosis through pregnane X receptor activation and the disruption of fatty acid transport and cholesterol biosynthesis [24].

While undoubtedly a subset of patients continues to experience the metabolic effects of lipodystrophy even years after discontinuing these drugs, they are now thankfully a small minority of modern cohorts of PLWH, and modern regimens with integrase inhibitors appear to be more metabolically friendly. Indeed, in a small randomized controlled trial, switch to raltegravir from efavirenz has shown to reduce liver steatosis [25,26].

The D:A:D cohort has shown that short-term gain in BMI following ART initiation increases the longer term risk of diabetes regardless of pre-ART BMI [27], somehow exceeding a simple 'return to health' phenomenon [28]. This observation has been characterized more recently in PLWH initiating ART with integrase inhibitors (INSTI) [28]. In a large well characterized ART naïve cohort, among 1,152 PWH, 356 initiated INSTI-based regimens. At all examined study time points, weight gain was highest among PLWH starting dolutegravir. At 18 months, PLWH on dolutegravir gained 6.0 kg, compared to 2.6 kg for subjects on non-nucleoside reverse transcriptase inhibitors (NNRTI) ($p<0.05$), and to 0.5 kg for those on elvitegravir ($p<0.05$) [28]. Similar findings were described in experienced PLWH switching to INSTI [29]. Nevertheless, metabolic consequences of weight gain after INSTI initiation are still controversial, and whether this will impact the risk of NAFLD in PLWH is unclear [30–32], (Figure 1).

Important unanswered questions remain. First, there is no longitudinal data evaluating long-term outcomes of PLWH and NASH. Cross-sectional studies are suboptimal in the assessment of disease severity and dynamics, while the requirement for a liver biopsy and

retrospective design of most studies introduce significant selection bias. Therefore, biopsy studies in PLWH have shown very variable rates of NASH (see prevalence of NASH in Table 1 in studies with available liver biopsy), similar to those in the general population [10]. Observational studies with histologically confirmed disease and outcomes after 10-15 years are required to understand more clearly the trajectory of NASH in PLWH. Second, although the metabolic syndrome is integral to NASH pathogenesis, more data is required on the secondary role of ART exposure and HIV chronic inflammation in this process.

NASH treatments which block, possibly in synergistic mechanism, steatosis and fibrosis progression, may improve this liver disorder, but has also the potential to reduce the burden on NICMs, particularly relevant in PLWH.

These issues can begin to be addressed through inclusion in clinical trials in which prospective, per-protocol paired liver biopsies are included in the trial design. In the general population such trials, particularly those with negative outcomes, have been invaluable in deepening our insight into the natural history of NASH [33]. Including PLWH as a sub-population will also provide an opportunity for well-matched comparisons with HIV negative subjects.

Current trials for NASH in HIV

Few pilot studies have addressed NASH treatment in HIV.

Lifestyle changes, with particular focus to physical activity and diet, are the first-line therapy in NAFLD/NASH in the general population. Weight loss of 10% is associated with resolution of steatohepatitis and improvement of fibrosis in a substantial number of patients [34]. In PLWH, studies have shown that higher intensity of physical exercise is needed to obtain similar metabolic improvements to the general population [35], while the effect on NAFLD/NASH has not been reported.

In the context of HIV-associated lipodystrophy, the use of pioglitazone, a thiazolidinedione insulin sensitising agent, has been shown to reduce liver fat, lobular inflammation, but fell short of achieving the primary endpoint of improvement or resolution of NASH [36] (Table 3).

The ARRIVE trial, a double-blind, randomized, placebo-controlled trial tested the efficacy of 12 weeks of treatment with aramchol versus placebo in 25 HIV-associated NAFLD. Over a 12-week period, hepatic-fat or change body fat and muscle composition did not change as assessed by utilizing novel MRI-based assessment in patients with HIV-associated NAFLD [37] (Table 3).

A recently published phase 4 open-label clinical trial included 27 mono-infected PLWH with NASH treated with vitamin E 800 IU daily for 24 weeks. The study found a decrease in inflammation assessed with ALT (-27 units/L), steatosis estimated by controlled attenuation parameter (-22 dB/m) and hepatocyte apoptosis with CK-18 (-123 units/L). These results are encouraging, but once again treatment with vitamin E did not improve liver fibrosis. At present, vitamin E treatment may be considered as a bridge therapy only, while waiting for availability of new drugs combination simultaneously addressing steatosis and fibrosis [38] (Table 3).

A particular case is represented by tesamorelin, a synthetic form of growth-hormone-releasing hormone, which is FDA approved for the treatment of excess abdominal fat in HIV-associated lipodystrophy. In a randomized, double-blind, multicenter trial including 61 PLWH with NAFLD, Stanley et al. assessed its effect on liver fat and histology. At baseline, liver biopsies revealed that 43% of patients had liver fibrosis and 33% had NASH. After 12 months of treatment, liver fat in patients on tesamorelin had decreased by 32% from baseline while it had increased by 5% in placebo patients (p=0.02), amounting to a 37% relative reduction in liver fat. Furthermore, 35% of patients in the tesamorelin group returned to liver fat values below 5% in comparison to only 4% of patients on placebo (p=0.007) [39]. The study also concluded that 10.5% of patients in the tesamorelin group experienced progression of liver fibrosis compared to 37.5% in patients receiving a placebo (p=0.04) [39] (Table 3). The DDI potential of tesamorelin has been evaluated with simvastatin, a cytochrome P4503A4 (CYP3A4) sensitive substrate, and the HIV protease inhibitor ritonavir. Tesamorelin (2 mg, multiple doses) was shown to have a minimal effect on simvastatin (80 mg) and ritonavir (100 mg) pharmacokinetics in healthy volunteers [40], suggesting that tesamorelin is unlikely to alter the exposure of antiretroviral drugs (see table 2). Since tesamorelin induces the secretion of growth hormone, concerns have been raised that CYP expression and/or activity may be modulated by growth hormone. However, growth hormone was shown to have no significant effect on CYP2D6 and CYP3A4 activity (CYPs contributing the metabolism of several antiretroviral drugs) in a randomized,

double-blind, placebo-controlled clinical study in which individuals received injections of growth hormone or placebo [41].

In a retrospective cohorts study maraviroc, a CCR5 antagonist, has shown a potential protective role to reduce the incidence of NAFLD in PLWH [42] (Table 3). A randomised pilot study is currently ongoing to assess its efficacy in an add-on antiretroviral therapy strategy over 48 weeks in HIV-1 monoinfected patients with NASH [43].

All together, these studies are too small to impact clinical practice or guidelines consideration at this stage.

Investigational agents for NASH and potential drug-drug interactions in the context of HIV

As the clinical phenotype of NASH in PLWH increasingly mirrors that of the general population, it could be considered that the treatment of NASH in PLWH would likely have the same etiological targets as in the general population. An increasing number of agents are being investigated for the treatment of NASH and many registrational trials are ongoing. In this setting, it is striking that PLWH have consistently been excluded from these studies. We are concerned that this may limit therapeutic options for NASH in PLWH. Pharma and sometimes regulatory agencies justify the exclusion of PLWH due to the risk of DDIs associated with concomitant chronic exposure to ART.

This concern can be addressed by conducting properly designed studies aiming to evaluate DDIs between novel compounds to treat NASH and ART. Furthermore, for some of these novel compounds available pharmacological data allows researchers to predict the likelihood of having DDIs with ART. The DDI profiles of these compounds can be summarized in tables, thereby providing an overview of the DDI risk within a therapeutic class similarly to what has been done with other drugs to treat NICMs (www.hiv-druginteractions.org; www.hep-druginteractions.org).

This section explores potential DDIs between ART and 5 drugs in the pipeline which are in phase III trials for NASH, thus being the most likely candidates to be approved for clinical use in the near future: aramchol, cenicriviroc, elafibranor, obeticholic acid and resmetirom (MGL-3196).

Aramchol

Aramchol is a fatty acid-bile acid conjugate inhibiting stearoyl coenzyme A desaturase 1 (SCD1), an enzyme playing a role in lipid metabolism. The inhibition of SCD1 results in decreasing synthesis of fatty acids, with consequent decrease in storage triglycerides and other esters of fatty acids. This reduces liver fat, including triglycerides and free fatty acids, resulting in an improvement in insulin resistance [44].

Information on the potential of aramchol to cause DDIs is currently not available, although there is an ongoing trial evaluating CYP3A4 inhibition of by aramchol [45]. Thus, the risk for DDIs with drugs undergoing mainly hepatic metabolism cannot currently be established.

Cenicriviroc

Cenicriviroc is a CCR5 and CCR2 CCR5/CCR2 antagonist. CCR5 and CCR2 are chemokine receptors expressed on circulating monocytes, as well as on Kupffer cells. Activation of these receptors induces migration of macrophages into the liver [44]. It was initially developed as an HIV drug [46], but it was shown to reduce the rates of hepatic fibrosis.

Cenicriviroc is currently investigated in NASH patients due to its anti-inflammatory and anti-fibrotic potential at an oral dosage of 150 mg daily.

Cenicriviroc is metabolized by CYP3A4 and CYP2C28 and is a substrate of P-glycoprotein. Cenicriviroc is devoid of strong inhibitory or inducing effects on drug metabolizing enzymes. DDI studies with dolutegravir (50 mg once daily) showed no significant effect on dolutegravir exposure whereas cenicriviroc exposure was reduced by 29% [47]. It is currently unclear whether this decrease in exposure would require a dosage adjustment of cenicriviroc. The coadministration with atazanavir/ritonavir (300/100 mg once daily) increased cenicriviroc (50 mg once daily) exposure by 289%. Hyperbilirubinemia was observed following coadministration of atazanavir/ritonavir with cenicriviroc. Similarly, coadministration with darunavir/ritonavir (800/100 mg once daily) increased cenicriviroc (50 mg once daily) exposure by 213%, however no clinically relevant laboratory abnormalities were observed [48]. Finally, coadministration with efavirenz (600 mg once daily) reduced cenicriviroc (200 mg once daily) exposure by 43% whereas cenicriviroc exposure was not significantly reduced when doubling cenicriviroc dose (400 mg once daily) [49].

Elafibranor

Peroxisome proliferator-activated receptors (PPARs) are transcription factors involved in lipid metabolism. PPARs are implicated in fatty acid catabolism. Elafibranor is a PPAR-alpha/PPAR-delta agonist. PPAR-alpha activation increases lipolysis cellular lipid uptake. In animal models, PPAR-delta activation leads to fatty acid consumption in skeletal muscle and adipose tissue [44].

Information on the metabolic pathway of elafibranor is not available from the public domain, except the fact that elafibranor is metabolized to GFT1007 [50].

Obeticholic acid

Obeticholic acid (Ocaliva®) is a bile acid analogue which is conjugated with glycine or taurine in the liver and secreted into the bile. Obeticholic acid is a semi-synthetic farnesoid X nuclear receptor (FXR) agonist. FXR is a bile acid receptor that regulates lipid and glucose metabolism and its activation leads to reduction in serum and hepatic triglyceride levels [44].

Concomitant medications to obeticholic acid that inhibit canalicular membrane bile acid transporters, such as bile salt export pump (BSEP), may exacerbate accumulation of conjugated bile salts including taurine conjugate of obeticholic acid in the liver, which may cause clinical symptoms. Thus, in case of coadministration with BSEP inhibitors [51], serum transaminases and bilirubin should be monitored (Ocaliva Product label). Although obeticholic acid was shown to inhibit CYP3A4 *in vitro*, a DDI study has demonstrated no clinically significant inhibition of CYP3A4 at the doses of obeticholic acid in clinical use [52]. Obeticholic acid is not expected to significantly inhibit or induce other cytochromes or drug transporters (Ocaliva Product label).

Resmetirom (MGL-3196)

Resmetirom is an agonist of the thyroid hormone receptor-β [53]. There is no information on the metabolic pathway of resmetirom, except that it is taken into the liver by hepatic transporters. Thus, potential DDIs with boosted ART regimens cannot be excluded. DDIs studies have shown no significant effect of resmetirom on statins exposure suggesting that resmetirom is unlikely to affect ART [54].

Table 2 summarizes the predicted risk of DDIs between selected antiretrovirals and drugs to treat NASH.

In the absence of randomized clinical studies, it is difficult to predict which therapeutic strategies would be more suitable in PLWH. From a theoretical point of view, it can be hypothesized that lean NAFLD associated with d-drug exposure would benefit more from a drug strategy focused on anti-oxidative stress aiming to improve mitochondrial dysfunction. On the other side, the pathogenesis and thus therapeutic target for NAFLD/NASH in PLWH with obesity and/or diabetes mellitus, may be similar to the general population. With this regard, a number of studies of animal models and human trials have evaluated the effects of glucagon-like peptide-1 receptor agonist (GLP-1RAs) on liver fat content and suggest that the treatment could represent a new alternative for NAFLD management [55]. However, the hypothesis that such treatments have a direct effect on hepatocytes is still questionable and there is no evidence that the positive effect of GLP-1RAs is linked to the presence of GLP-1R on hepatocytes [56]. In HIV setting, there is an ongoing randomized double-blinded, placebo controlled trial to assess effect of semaglutide on visceral and ectopic fat in HIV-associated lipohypertrophy [57].

With regard to dyslipidaemia, frequently PLWH with NAFLD are qualified for statin therapy. It is hypothesized that treatment with statins may have beneficial effects on NAFLD and its liver-related complications, exerting systemic pleiotropic mechanisms, that collectively may concur in improving steatosis, sterile inflammation, fibrosis and tumorigenesis, nevertheless these evidences are still lacking [58].

Lessons from Direct-Acting Antiviral (DAA) Trials in HIV/HCV Co-infection

So, how do we move forward towards the safe inclusion of PLWH into NASH trials? The phenomenally successful development of safe and effective drugs against the HCV that included HCV/HIV co-infection could provide a helpful paradigm from which to draw lessons to inform our approach to NASH in PLWH.

The natural history of HCV/HIV co-infection was known to behave differently that HCV mono-infection, characterised by more rapid fibrosis progression [59]. In the early studies on pegylated interferon (PEG-IFN) and ribavirin, response rates were much lower in PLWH, perhaps, among other mechanisms, linked to the significant immune dysregulation in patients with

advanced and inadequately treated HIV [60]. Therefore, the registration trials for PEG-IFN only occurred some years after the trials leading to its licensing in HCV mono-infection.

The early trials in the DAA era with the protease inhibitors boceprevir and telaprevir responded to this uncertainty over response and dosing following the experience with PEG-IFN with designing trials of longer duration with the same doses [61]. However, ribavirin/sofosbuvir studies set the benchmark for designing trials that continued to separate patients with HIV co-infection but used the same duration and dosing as in trials on mono-infection [62]. This has remained the most common approach, expediting registration trials in HCV/HIV co-infection and demonstrating the diminished influence of ART or HIV itself on treatment safety and efficacy.

Taking it one step further, the Zepatier® combination- Elbasvir and Grazoprevir- included subjects with HCV/HIV co-infection within the main registration trial and built in an *a priori* analysis of the sub-group with HIV when designing the power of the study [63].

Therefore, as the quality of the drugs available improved, the relevance of HIV in the delivery or efficacy of the interventions diminished such that there was much closer alignment with this population in the introduction of DAAs for HCV.

A Way Forward for PLWH in NASH Trials

How can these lessons inform trial design for NASH in HIV? As in HCV/HIV, there is some data to support additional pathophysiological mechanisms in HIV-associated NASH, including ART effects on lipid metabolism, particularly, but not exclusively, with respect to those patients subjected to now obsolete drugs strongly associated with lipodystrophy. However, since the clinical phenotype is so strongly associated with the metabolic syndrome, the pathways leading to liver injury, NASH and fibrosis (e.g. insulin resistance, adipose-derived inflammation and impaired lipid metabolism) remain those targeted by many current therapies under investigation. It would therefore be reasonable to expect similar response rates between those with and without HIV.

Therefore, for drugs where there is a low probability of DDIs, PLWH may be included as a pre-specified sub-group within a trial population. To allay concerns from the pharmaceutical industry about delays in licencing for the general population, PLWH can then be excluded from the interim analysis much like other trials have included F1 fibrosis stage as a group of interest

but focused on F2/3 in the interim analysis. Where significant uncertainty exists over potential DDIs, mainly driven by booster containing regimens, small exploratory studies can be readily conducted to answer this question before proceeding to inclusion in larger trials.

This approach, in contrast to separate trials on HIV-associated NASH, is particularly important as the requirement for a liver biopsy makes it very difficult to recruit into adequately powered trials. A pre-specified sub-analysis within a larger trial would enable exploration into some unanswered questions on the pathophysiology and efficacy of new drugs in HIV-associated NASH, while expediting the licensing of new therapies in this population.

Conclusion

NASH is a common problem in aging populations of PLWH treated with ARVs. The predominating pathophysiological mechanisms are likely to be similar to the general population and closely related to the metabolic complications of obesity. PLWH are likely to similarly benefit from the therapeutic targets investigated in current trials, and where there is adequate knowledge of DDIs, they should be included as a pre-specified sub-population to improve the generalisability of the results and expedite the introduction of therapies in this population. Clinical trial data will also help address current gaps in the disease mechanisms and natural history of HIV-associated NASH.

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Conflict of interest

GG received research grant and speaker honorarium from Gilead, ViiV, MERCK and Jansen. He attended advisory boards of Gilead, ViiV and MERCK. JMa received honoraria for speaking at the HIV Clinical Updates course. ET has served in advisory boards for Intercept, Gilead, Pfizer and Promethera and was a speaker for Gilead and Intercept. JP reports research grant support from Gilead and Merck, speaker honorarium from Gilead, and spouse's ownership interest in Bristol-Myers Squibb, Johnson and Johnson, Merck, and Abbvie. CGM attending advisory board meetings for Theratechnologies. GS has acted as speaker for Merck, Novonordisk, Gilead, Abbvie, served as an advisory board member for Merck, Intercept, Gilead and Novartis and has received research funding from Merck, Theratec and Pfizer. KM, JMi and SB, CM, PI and ML reported no conflict of interest.

Authors contributions

GG, JMa and GS conceptualized and designed the manuscript. CM contributed with an expert opinion. GG, JMa, JMi, KM, CM, SB and GS wrote and revised the manuscript. GG, JMa, TE and GS did the supervision of the final version of the manuscript. All the authors contributed to discussion and revised the manuscript.

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Table 1. Prevalence of NAFLD and NASH in PLWH without viral hepatitis in various studies.

Author and year of publication	**Country / Design**	**N**	**Age** (years)	**Ethnicity** (%)	**Diagnostic procedure**	**BMI** (Kg/m^2)	**Diabetes** (%)	**Duration HIV infection** (years)	**Time on ART** (years)	**Elevated ALT** (%)	**NAFLD** (%)	**NASH** (%)	**Fibrosis prevalence (%)**
Benmassaoud A. (2018) [64]	Canada / Prospective	202	53.9+8.3	White (45.2); Black (37.6)	CAP/liver biopsy	27.7+4.5	7	19.9+7.4	NA	75	53.9	11.4	NA
Crum Cianflone N. (2010) [65]	USA / Prospective	216	41 (IQR 30-46)	White (47.7); Black (27.3)	Liver biopsy	26.0+4.1	5.1	14 (IQR 6-20)	NA	100	31	7.3	3.64
Guaraldi G. (2008) [66]	Italy/ Prospective	225	48.43+8.16	NA	CT	23.75+3.59	18.29	12.25+5	NA	NA	36.9	NA	NA
ngiliz P. (2009) [67]	France / Prospective	30	NA	NA	Liver biopsy	23.0+3.1	NA	13 (IQR 9-15)	NA	100	60	53.3	NA

Lemoine M. (2006) [68]	France / Prospective	14	43.5 (range 31-58)	NA	Liver biopsy	23.0+3.4	NA	10.6 (median)	NA	100	57.1	57.1	28.6
Lemoine M. (2019) [16]	UK / Prospective	402	54 (IQR 53-65)	White (82)	CAP/Liver biopsy	26 (IQR 24-30)	65 (insulin resistance)	NA	15 (range 13-18)	39	76	47	NA
Lombardi R. (2017) [69]	UK / Retrospective	156	47.5+8.5	NA	CAP/Liver biopsy	NA	11	14 (IQR 2-30)	11 (IQR 0-26)	100	65	NA	33
Lui G. (2016) [70]	China / Prospective	80	51.1+9	Chinese Asian (93.8%)	H-MRS	26.7+4.3	73.9	8.2+4.9	6.33+3.92	NA	28.75	NA	NA
Mohr R. (2018) [71]	Germany / Prospective	289	46 (20–75)	White (76.3); Black (15.1)	CAP	24 (15–41)	NA	9 (range 0-29)	7 (0-27)	NA	40	NA	NA
Morse CG (2015) [72]	USA / Prospective	62	50 (range 17-67)	White (65.0);	Liver biopsy	27.6 (range	9.7	17.5 (range 2.3-	12.9 (range	100	72.6	54.8	19.4

				Black (8.0)		15.3-47.1)		27.8)	1.7-22.8)				
Nishijima (2014) [73]	Japan / Prospective	435	43 + 11	East Asian 97.5%	Ultrasound	25 + 4.5	6.67	NA	6.33+3.92	100	31	NA	NA
Prat L. (2018) [74]	UK / Retrospective	97	47+10	Caucasian (66); Black (30)	Liver biopsy	27+6	11	10.5+9.3	8.3+7.2	100	28.7	8.2	20
Pembroke T. (2017) [75]	Canada / Prospective	538	50 (42-56)	White (52.1); Black (32)	CAP	25.4 (23.0-28.6)	25.1	13 (7-20)	13 (7-20)	NA	36	NA	18
Perazzo H. (2018) [76]	Brazil / Prospective	395	45 (IQR 35-52)	Black (53%)	CAP	25.7 (23.2-29.4)	10	10 (6-16)	7 (4-14)	NA	35	NA	9
Price J. (2017) [77]	USA/ Prospective	122	51 (IQR 57-57)	Caucasian (53%)	H-MRS	26 (IQR 24-30)	8.2	NA	7.9 (IQR 3.3-	NA	28	NA	NA

									12.5)				
Price J. (2017) [78]	USA/Prospective	329	52 (IQR 47-57)	Caucasian (55%)	CT	26 (IQR 23-29)	12	NA	9 (IQR 6-12)	NA	13	NA	NA
Sterling K. (2013) [79]	USA / Prospective	14	45+10	Caucasian (57)	Liver biopsy	29.9+7.4	0	NA	NA	100	64.3	28.6	35.7
Vodkin I. (2015) [80]	USA / Prospective	33	44.8+9.4	Hispanic (51.5)	Liver biopsy	29.8+6.0	18.2	NA	NA	NA	NA	63.6	33.3
Vuille-Lessard E. (2016) [8]	Canada / Prospective	300	49.6+9.5	White 42.0% Black 40.0% Others 18%	CAP	27.9+4.7	13.2	14.5+8.1	12.8+ 11.1	NA	48	NA	15

Legend: Continuous variables are expressed as mean + standard deviation or median (interquartile range or range) and categorical variables are presented as percentages. Abbreviations: ALT - alanine aminotransferase; ART - antiretroviral therapy; BMI - body mass index; CAP - controlled attenuation parameter; HIV - human immunodeficiency virus; IQR - interquartile range; NA - not available; NAFLD - non-alcoholic fatty liver disease; NASH - non-alcoholic steatohepatitis.

Table 2. Potential drug-drug interactions between selected antiretrovirals and drugs to treat NASH.

NASH drugs	Clinical trial phase	ATV/c	ATV/r	DRV/c	DRV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
Aramchol	III															↔	↔	↔	↔	↔
Cenicriviroc	III	↑	↑289%	↑	↑213%	↔	↓43%[a]	↓	↓	↔	↔	↔	↓29%	↑	↔	↔	↔	↔	↔	↔
Elafibranor	III															↔	↔	↔	↔	↔
Obeticholic acid*	III	↑	↑	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Resmetirom (MGL-3196)	III					↔	↔	↔	↔	↔	↔	↔	↔		↔	↔	↔	↔	↔	↔
Tesamorelin		↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

Colour legend

No clinically significant interaction predicted

Potential clinically significant interaction that may require dosage adjustment or clinical monitoring

The limited available data on drug metabolism do not allow to assess the risk for drug-drug interactions

Legend

↑ Potential elevated exposure of the NASH drug

↓ Potential decreased exposure of the NASH drug

↔ No significant effect

a = doubling cenicriviroc dosage allowed to compensate the drug interaction with efavirenz.

*For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, see:

http://www.hep-druginteractions.org (University of Liverpool).

Abbreviations

ABC - abacavir; ATV/c - atazanavir/cobicistat; ATV/r - atazanavir/ritonavir; BIC - bictegravir; DOR - doravirine; DRV/c - darunavir/cobicistat; DRV/r - darunavir/ritonavir; DTG - dolutegravir; EFV - efavirenz; ETV - etravirine; EVG/c - elvitegravir/cobicistat; FTC - emtricitabine; MVC - maraviroc; NVP - nevirapine; RAL - raltegravir; RPV - rilpivirine; TAF - tenofovir alafenamide; TDF - tenofovir disoproxil fumarate; 3TC - lamivudine

Table 3 depicts an overview of studies that examined NAFLD/NASH treatment in HIV.

Author and year of publication	Country and sample size	Study design	Diagnostic method for NAFLD/NASH	Treatment	Control group	Main finding
Matthews L, 2015 [36]	USA, 13 subjects with HIV/HCV coinfection	48-week, randomized, double-blind, placebo controlled trial	MRS imaging	Pioglitazone	Yes	Pioglitazone group had a significant decrease in hepatic fat from baseline (15.1 – 7.0%) to week 48 (7.6 – 3.9%), with a mean difference of -7.4% (p = 0.02, n = 5), while placebo group did not show any changes in hepatic fat content.
Ajmera VH, 2019 ARRIVE Trial [37]	USA, 50 subjects with HIV infection	12-week, double-blind, randomized, investigator initiated, placebo-controlled trial	MRI-technique in patients with HIV-associated NAFLD	Aramchol	Yes	Aramchol did not reduce steatosis or change body fat and muscle composition, over a 12-week.
Sebastiani G, 2019 [38]	Canada, 27 HIV-mono-infected patients	24-week, single center, open-label, single arm	NASH diagnosis was based on CAP ≥248 dB/m and cytokeratin-18 >130.5 U/L	Vitamin E	No	It was observed a decrease in inflammation assessed with ALT (-27 units/L), steatosis with controlled attenuation parameter (-22 dB/m) and hepatocyte

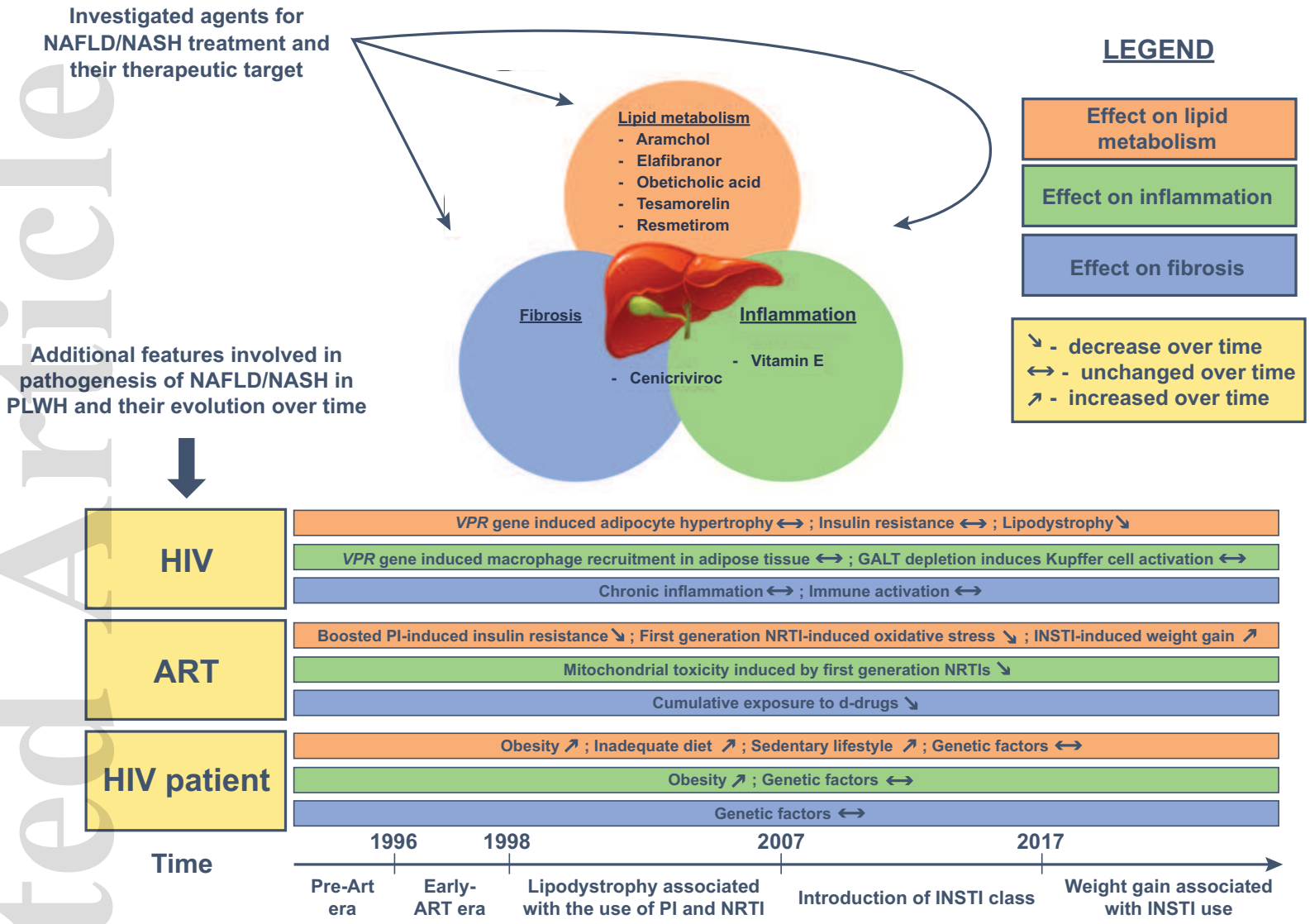
						apoptosis with CK-18 (-123 units/L)
Stanely T, 2019 [39]	USA, 61 PLWH	48-week, randomized, double-blind, multicentre trial	MRS imaging	Tesamorelin	Yes	After 12 months of treatment, liver fat in patients on tesamorelin had decreased by 32% from baseline, while it increased by 5% in placebo reducing liver fat for 37%
Piconi S, 2019 [42]	Italy, 312 PLWH	retrospective	Liver to spleen ratio assessed by CT	Maraviroc	No	Maraviroc has shown a potential protective role to reduce the burden of NAFLD in PLWH.

Abbreviations

ALT - alanine transaminase; CT – computed tomography; HCV – hepatitis C virus; HIV – human immunodeficiency virus; MRS - magnetic resonance spectroscopy; NAFLD – non-alcoholic fatty liver disease; NASH – non-alcoholic steatohepatitis; PLWH – people living with HIV

Figure 1 reviews the pathogenesis of NAFLD/NASH in PLWH and relative therapeutic targets for investigated agents for NAFLD/NASH treatment. Therapeutic targets are didactically divided into three groups: lipid metabolism, inflammation and fibrosis. Additional HIV-related features involved in NAFLD/NASH pathogenesis are grouped according to therapeutic targets. Timeline at the bottom depicts the most important historical time points in HIV and ART that have impacted the management of PLWH and their possible association with NAFLD/NASH pathogenesis.

Abbreviations: ART – antiretroviral therapy; GALT – gut-associated lymphoid tissue; HIV – human immunodeficiency virus; ; INSTI – integrase strand transfer inhibitors; NRTI – nucleoside reverse transcriptase inhibitors; PI – protease inhibitors; PLWH – people living with HIV; VPR – viral protein R.



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