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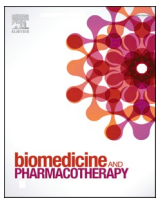

Review

The pathogenesis of metabolic dysfunction-associated steatotic liver disease and nucleoside reverse transcriptase inhibitors (NRTIs) -based HIV-antiretroviral regimens: A comprehensive narrative review

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ABSTRACT

Metabolically-dysfunction-associated steatotic liver disease (MASLD) is the result of fat accumulation in > 5 % of hepatocytes, given the absence of excessive alcohol consumption. The metabolic conditions, such as obesity with ectopic fat accumulation, serve as one of the risk factors of MASLD. The pathogenesis of MASLD may be attributed to the impaired systemic lipid metabolism as well as activation of *de novo* lipogenesis transcription factors, such as ChREBP and SREBP-1C, in the liver. The combined effects of both systemic dyslipidaemia and hyperactive hepatic *de novo* lipogenesis have been widely associated with the onset and progression of MASLD from steatosis to metabolic dysfunction-associated steatosis hepatitis (MASH). Moreover, systemic insulin resistance and impaired hepatic insulin function also correlate with the onset of MASLD. People living with HIV (PLWHIV) have been reported to be more susceptible to the development of MASLD. However, whether this could be attributed to the chronic use of antiretroviral therapy treatments (ART) or the detrimental effects of the virus remains the subject of research. Over the past decades, different regimens of ART, including highly active antiretroviral therapy (HAART), have been introduced. However, some of the HAART regimen drugs are continually being discontinued citing a variety of side effects, including metabolic derangements. Furthermore, the recent developments on GLP-1 agonists showing the cardioprotective and antidiabetic effects have elicited increasing interest in their potential repurposing for the treatment of MASLD. The preventative measures for MASLD will be imperative in the future, and this may include constant monitoring of hepatic de novo lipogenesis markers in individuals on chronic medications such as ART

Aim and Scope of the Review

The association of ARVs with metabolic disturbances such as systemic insulin resistance and dyslipidemia has led them to be placed among the predisposing risk factors for MASLD. Pharmacotherapies are at the center of HIV prevention and management strategies that are employed by the world health organization and other affiliated health bodies. This indicate that for as long as the cure for HIV has not been discovered, a significant number of the world's population will rely on ARVs for better health outcomes. Previous studies have reported that people living with HIV (PLWHIV) has higher chances of developing MASLD, however, whether this can be attributed to lifestyle, HIV or ARVs still remains a subject of research. This leaves us with the question: What effects do ARVs have on the development of MASLD onset? Hence, this review aims to explore the impact of antiretroviral drugs on the pathogenesis of Metabolic dysfunction-associated steatotic liver disease.

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is metabolic condition is characterised by hepatic fat accumulation, also known as steatosis, exceeding 5 %-10 % by mass without the excessive use of alcohol [1–5]. approximately 25 % of the world's population is affected by this clinicopathological syndrome [6,7]. This might be due to the increasing prevalence of other predisposing metabolic conditions such as type-two diabetes mellitus (T2DM) and obesity [2,7,8]. Furthermore, other risk factors that have been reported to contribute to MASLD development, include overindulgence in high-calorie diets,

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genetic susceptibility, epigenetics, and auto-immune disorders [9,10]. However, chronic treatments including HIV antiretrovirals have also been identified as some of the potential risk factors contributing to the development of MASLD. In addition, the prevalence of MASLD in people living with HIV (PLWH) is approximately 50 %-65 %, making the use of chronic ART a potential contributing factor to the development of MASLD [1,11–13]. Previous regimens of HIV- antiretroviral therapy have been associated with complications such as ectopic fats accumulation, imparted glucose tolerance and hyperlipidaemia, alluding to the possibilities of ARVs to involved in the pathogenesis of MASLD [14]. The treatment duration might be one of the determining factors linking HIV-ARV and the onset of MASLD in PLWH [11,12]. Although previous studies have alluded on the strong association between hepatic fat accumulation and impaired hepatic insulin signalling, the causative effects remains the subject of research [12,15] Moreover, in PLWHIV, this association is more prevalent than in healthy individuals [15] Current ART regimens have shown a much improved metabolic toxicity compared to earlier regimens [5]. However, these newly formulated regimens still has remnants of the ARV classes that were earlier discontinued such as nucleotide reverse transcriptase inhibitors (NRTIs) and Non-nucleoside reverse transcriptase inhibitors(NNRTIs). This leaves a question about the potential NRTIs interacting with metabolic hormones or their receptor and hence altering their physiological functions. Thus, this review encapsulates the potential, as well as the known effects of fixed-dose ARVs on the multifaceted pathophysiological mechanisms underlying the development of MASLD, including, but not limited to, oxidative stress, inflammation, hepatic insulin resistance, lipid accumulation, and systemic metabolic disruption [16].

2. Metabolic dysfunction-associated steatotic liver disease

Metabolic dysfunction-associated steatotic liver disease(MASLD), previously known as non alcoholic fatty liver disease(NAFLD), develops over virous stages including metabolic dysfunction associates steatosis liver (MASL), metabolic dysfunction associates steatohepatitis (MASH), hepatic fibrosis, and ultimately, hepatic cirrhosis [17,18]. The nomenclature for fatty liver disease has recently been changed from non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) to metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH), respectfully, to more precisely encapsulate the metabolic foundations of the disease, as well as to eliminate the exclusion of alcohol consumption as a defining factor [19]. Globally, MASLD affects 32–38 % of adults, with this prevalence predicted to increase to 55–60 % by 2040, as a result of the global rise in sedentary lifestyles and obesity [18,20,21]. Although data is limited, the prevalence of MASLD ranges between 10 % and 28 % in sub-Saharan Africa, with prevalence rates of approximately 23 % in men and approximately 27 % in women [18]. In South Africa, the rising diabetes and obesity trends suggest rapidly growing prevalence rates, subsequently illuminating the fact that MASLD is a growing public risk challenge [22]. The key risk factors include T2DM, insulin resistance, obesity, dyslipidaemia, older age, high-fructose diets, as well as genetic variants such as TM6SF2 and PNPLA3 [22,23]. The Pathophysiology of MASLD includes mitochondrial dysfunction, chronic inflammation, oxidative stress, and adipose tissue insulin resistance. These metabolic derangements are associated with increased hepatic influx of free fatty acids and activation of hepatic *de novo* lipogenesis through insulin and mTOR/SREBP-1c and glucose/ChREBP pathways [23,24]. These factors create a vicious cycle that promotes the progression of MASLD to fibrosis, and possibly, cirrhosis [23,24].

2.1. Metabolic dysfunction- associated steatotic liver

Steatosis is medically defined as the intrahepatic triglyceride retention and accumulation in > 5 % of hepatocytes and is classified as the earliest stage of MASLD [25]. Histological evaluation shows that steatosis is characterised by the presence of large lipid droplets that displace the nucleus within hepatocytes, and frequently remains asymptomatic during its initial stages [8]. Under normal physiological conditions, hepatic lipid homeostasis is maintained via a balance between the uptake of fatty acids, fatty acid oxidation, *de novo* lipogenesis (DNL), and the secretion of very low-density lipoprotein (VLDL) [26,27]. Abnormal lipid metabolism is shown to be prevalent among individuals with T2DM [27]. There are multiple sources of hepatic fatty acids, including FA release from adipocytes through lipolysis, from dietary fat consumption, and de novo liver lipogenesis [20,28]. When any of the triacylglycerol pathways regarding the synthesis, transport, or oxidation are disrupted, the hepatic accumulation of fat deposits increases [20,29]. It has been reported that there is an increased prevalence of hyperlipidaemia among HIV-infected individuals who receive ARVs, as shown by the increased blood lipid profiles of HIV-infected individuals [30]. Studies have reported that decreased levels of hepatic glycogen lead to an increase in fat build-up in the liver (steatosis), which is suggested to play a role in hepatic insulin resistance [30,31]. The systemic and hepatic insulin resistance(IR) has been implicated in the disruption of liver fatty acid homeostasis [32]. Chronic IR has been closely associated with the activation of the SREBP-1c and ChREBP pathways, which favour the DNL. Furthermore, IR has also been associated with adipose tissue lipolysis, which results in an elevated influx of free fatty acids (FFAs) into the liver [32]. The IR-induced adipose tissue dysfunction is characterised by the reduced plasma adiponectin, an adipokine that has been reported as an insulin sensitiser and FA oxidation regulator. The reduction of adiponectin further exacerbates the accumulation of intrahepatic lipids, leading to the onset of steatotic liver [26,33]. The previous studies have associated the chronic use of some antiretroviral therapy (ART) regimens containing NRTIs with dyslipidaemia and mitochondrial dysfunction. However, whether NRTI-based ART regimens are associated with hepatic IR and the subsequent onset of steatotic liver remains unclear. Fig. 1

2.1.1. Hepatic de novo lipogenesis-driven steatosis

De novo lipogenesis (DNL) is the internal enzymatic process by which dietary carbohydrates (starch and sugars, such as glucose) are converted into fatty acids [29,34]. These fatty acids can either enter the energy generation mechanisms or be stored as TGs various tissues including the liver [28]. The hepatic DNL pathway is regulated by nutrient and oxysterol sensing through liver X receptors (LXR). Moreover, transcription factors such as carbohydrate response element protein (ChREBP) and sterol regulatory element-binding protein-1c (SREBP-1c) are also the drivers of the enzymatic hepatic DNL [35]. The regulatory enzymes that regulate hepatic DNL include acetyl-CoA carboxylase (ACC), FA elongase 6, FA synthase (FAS), and stearoyl-CoA desaturase (SCD), which drives the FA synthesis [35]. Hence, any disruption in the expression or activity of these enzymes impacts the hepatic DNL, i.e the acetyl-CoA carboxylation catalysed by ACC, subsequently leading to the synthesis of saturated FAs [36]. In addition, FAS is also play a pivotal role in the synthesis of palmitic acid, a saturated FA that has been implicated in the development of insulin resistance [37]. Palmitate, or palmitic acid, is the most abundant saturated long-chain FA in the human body [38]. However, whether present or past NRTIs regimens activate FAS, leading to the elevation of palmitic acid and subsequently the onset of insulin resistance, remains underexplored. Enhanced DNL contributes to increased fat mass and hepatic fat accumulation, which is associated with the development of MASLD [35]. The *de novo* synthesis of FAs and TGs from the surplus of carbohydrates occurs primarily in the liver, as depicted in Fig. 2 [39].

2.1.2. Carbohydrate response element-binding protein and HIV-related hepatic steatosis

Carbohydrate response element-binding protein (ChREBP) is the transcription factor that identifies excessive dietary carbohydrate

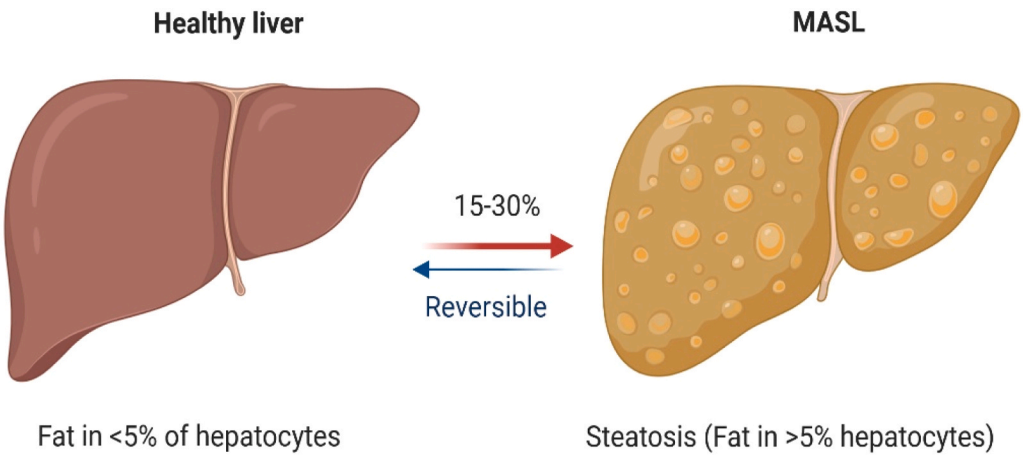

Fig. 1. The hepatic *de novo* lipogenesis, from simple carbohydrates to triglycerides.

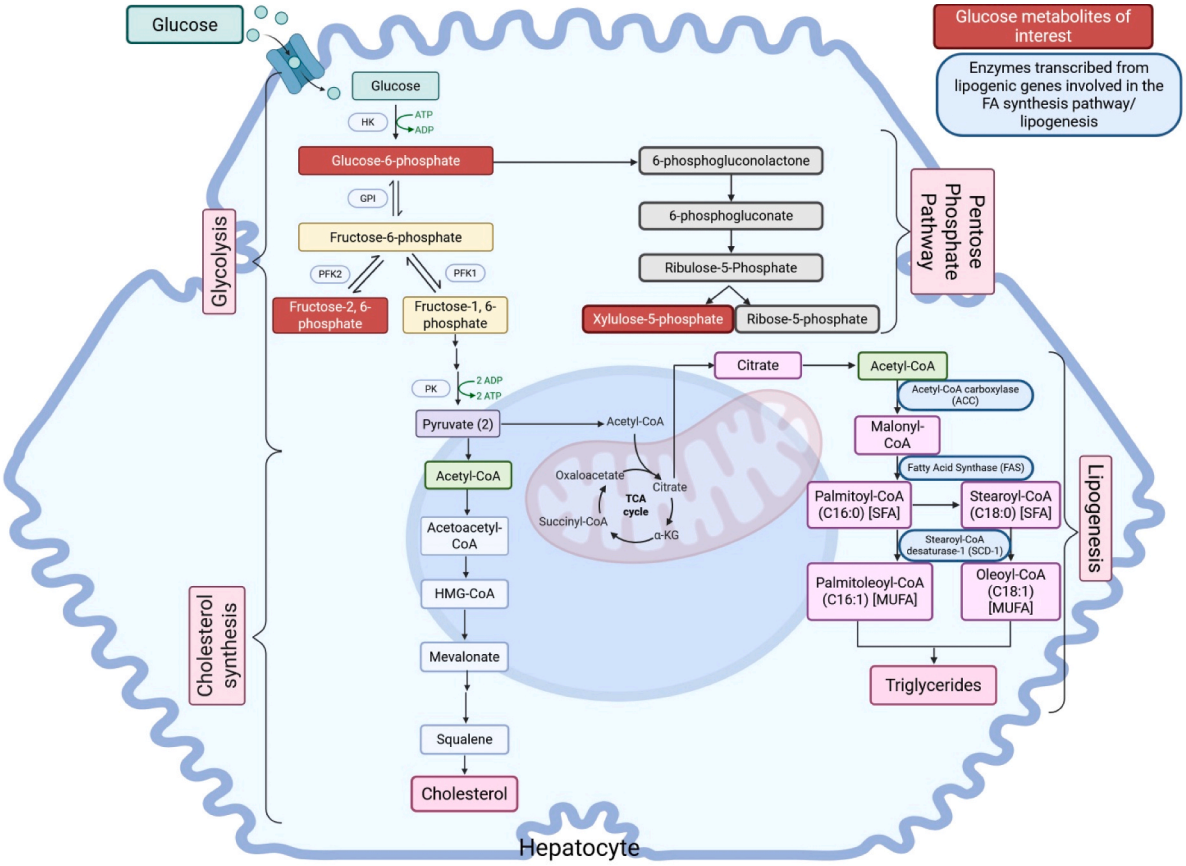

Fig. 2. The hepatic *de novo* lipogenesis, from simple carbohydrates to triglycerides.

intake, particularly glucose, which subsequently triggers glycolysis, lipogenesis, glycogen synthesis, as well as the pentose phosphate pathway, which, together, contribute to an accelerated reduction in systemic blood sugar levels [40–42]. This singular transcription factor has the ability to transmit glucose-dependent lipogenic and glycolytic signals and is generally dispersed across various types of cells, including hepatocytes, adipocytes, intestinal cells, muscle cells, brain cells, and pancreatic β-cells [40,41,43]. Furthermore, ChREBP also inhibits lipolysis and promotes the efficient translocation of excess hepatic triglycerides to adipocytes [40,41,44]. The hepatic glucose-induced activation of ChREBP includes multiple mechanisms such as allosteric modification and protein phosphatases activation 2 A, [40,41]. A glucose-derived metabolite glucose-6-phosphate (G6P) has been reported to promote both activation and transcription of ChREBP. This is through the promotion of the translocation to the nucleus. Moreover, xylulose-5-phosphate (X5P), an intermediate metabolite of, has also been shown to promote the transactivation of ChREBP via phosphorylation or allosteric modification [40,41,43]. The transcriptional targets of ChREBP include genes that are involved in the synthesis of fatty acids (ACC, SCD-1 and FASN) [40,41]. Liver-pyruvate kinase (LPK) is also regulated by ChREBP, subsequently contributing to the promotion of glucose disposal [40,41]. Liver biopsies from individuals with early-stage MASH have shown that elevated expression of ChREBP is a feature that is regularly observed [40,41]. Research conducted on obese

mouse models has also shown that the reduction of ChREBP expression levels is linked to the alleviation of hyperinsulinemia and hyperglycaemia, while also exhibiting that the presence of this transcription factor contributes substantially to hepatic steatosis [40,41]. A direct link between ChREBP and hepatic steatosis development can be seen in individuals living with HIV, which is supported by the observations that have demonstrated that HIV patients can develop hepatic steatosis via ChREBP [40,41]. More specifically, studies in which male mouse models that have been infected with HIV, have exhibited that the nuclear levels of ChREBP in hepatocytes were increased by the HIV-1 accessory protein, while the signalling activity of Liver X Receptor-α (LXRα) was also elevated [40,41]. As a result of these overactive pathways, inflammation and *de novo* lipogenesis was shown to be increased, which subsequently contributes to the onset of hepatic steatosis, ultimately directly implicating ChREBP in MASLD/MASH progression in PLWHIV [40,41]. Fig. 3

2.1.3. *Sterol regulatory element-binding protein-1c and hepatic steatosis*

Sterol Regulatory Element-Binding Protein-1c (SREBP-1c) serves as a principal regulator of the complete metabolic pathway governing cholesterol and fatty acid biosynthesis in the liver [40,45]. This transcription factor selectively stimulates the transcriptional functions of genes that are pivotal for the biosynthesis of fatty acids without exerting a substantial effect on the transcription of the genes that are associated with cholesterol production [40,45]. Another factor that influences the transcriptional control of SREBP-1x is liver X-activated receptors (LXRs), more specifically the LXRα and LXRβ isoforms, which are activated by oxysterol metabolites, subsequently bind to a locus within the SREBP-1c promoter, leading to the direct stimulation of SREBP-1c transcriptional activation [40,45]. This LXR-mediated activation significantly elevates the biosynthesis of fatty acids by stimulating SREBP-1c [40,45]. Polyunsaturated fatty acids (PUFAs) are also considered to be a factor that influences the transcriptional control of SREBP-1c, as they exert their inhibitory effect on the transcription of SREBP-1c by preventing the activation of LXR, while concurrently increasing SREBP-1c mRNA degradation, consequently contributing to a decrease in the concentrations of plasma triglycerides [40,45]. This key transcription factor is severely implicated in the pathogenesis of MASLD/MASH, as well as hepatic insulin resistance, which is demonstrated in experimental models of insulin resistance, like the obese (ob/ob) murine model showing hyperinsulinemia which elucidates the fact that the SREBP-1c levels are substantially increased in fatty liver tissues [40,45]. Even in the presence of peripheral insulin resistance, the persistent activation of SREBP-1c leads to the elevated expression of the genes that are involved in the production of lipids, increased synthesis of fatty acids, as well as the abnormal hepatic triglyceride accumulation, which are considered as hallmarks of MASLD [40,45]. The SCAP/SREBP pathway, which controls the activity of SREBP-1c, is reasoned to be pivotal in the development of carbohydrate-induced hypertriglyceridemia, and diabetic-induced MASLD [40,45]. Therefore, by targeting the activation of SREBP, potential therapeutic options are offered for the treatment of MASLD [40,45]. The development of hepatic steatosis, which is a component of MASLD/MASH, has been linked to SREBP-1c in PLWHIV, which is supported by previous studies that have been conducted on HIV-infected mouse models that have demonstrated that the HIV-1 Vpr accessory protein activates fatty liver via a mechanism that involves enhanced signalling of LXRα, which includes SREBP-1c activation [40,45]. This unrestricted activation substantially amplifies hepatic de novo lipogenesis, which, together with elevated inflammatory processes,

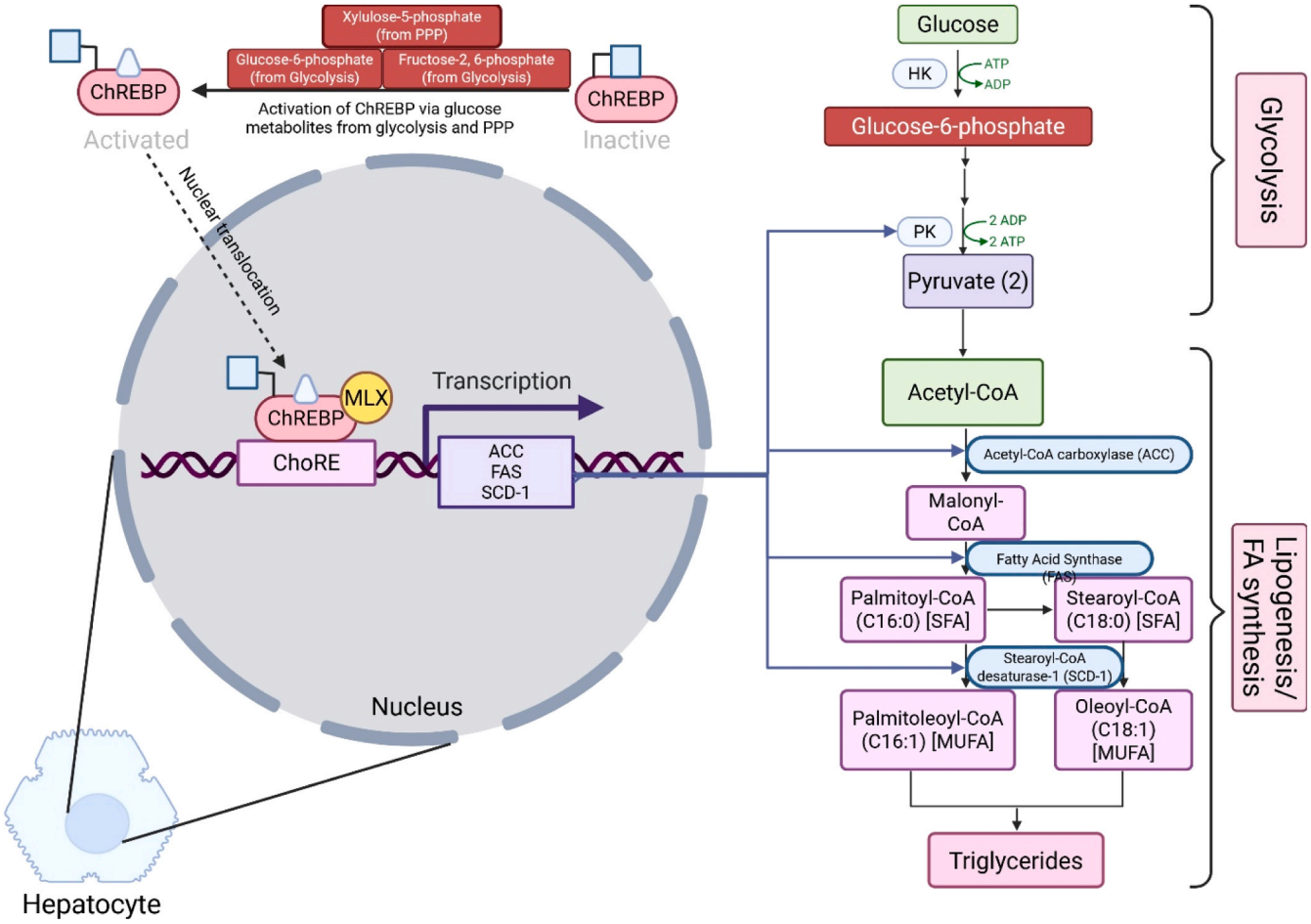

Fig. 3. The involvement of ChREBP in hepatic *de novo* lipogenesis.

results in the development of hepatic steatosis [40,45]. This direct activation of the LXRα/SREBP-1c axis via factors that are related to HIV, accentuates the role that SREBP-1c's play in liver disease in individuals with HIV, more specifically in individuals with concomitant insulin resistance [40,45]. Fig. 4

2.1.4. Cholesterol and de novo lipogenesis

The liver X receptors(LXRs) are activated by insulin and various sterols (such as oxysterols), which are cholesterol derivatives that have a hydroxyl group-containing side chain, and have been shown to increase both ChREBP and SREBP-1c transcription [46]. Thus, LXR deficiency results in decreased SREBP-1c and FA biosynthesis expression [46]. Both isoforms of LXRs, i.e LXRβ and LXRα, the mammalian isoforms, which are nuclear receptors that play key roles in the control of lipid metabolism by regulating transcriptional control [47]. These nuclear receptors form heterodimers with retinoid X receptors, which bind to the appropriate ligand to subsequently activate target gene expression [48]. The ligand to which the heterodimers bind is LXR response elements (LXREs) located in the target genes' regulatory regions [47]. The suppression of the lipogenic gene expression occurs when the LXR-RXR heterodimer complex binds co-repressors in the absence of the appropriate ligands [47]. Synthetic ligands or oxysterols activate LXRs to stimulate target gene expression of the genes that are involved in lipid metabolism [47]. Consequently, the LXRα target gene mRNAs that are implicated in lipogenesis were found to be overexpressed in individuals with MASLD [27]. This is supported by the abnormally enhanced hepatic LXRα expression, as well as its associated inflammatory and lipogenic genes that are observed in individuals with MASLD presenting with steatosis [27]. Thus, suppressing the activation of LXRα may be valuable in the endeavour to treat individuals with MASLD [27]. Moreover, high-fat diets alone, in addition to LXRs, induce the expression of SREBP-1c, subsequently resulting in lipogenesis [35]. As persistent steatosis advances, the combined effects of metabolic stress and LXR-mediated lipogenesis may induce hepatocellular injury, inflammatory signalling, and immune activation, which are all pathological hallmarks that define the progression from MASLD to MASH [49,50]. . Fig. 5

2.1.5. Metabolic dysfunction-associated steatohepatitis

Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive inflammatory characteristic within the broader spectrum of MASLD, distinguished by hepatic steatosis accompanied by hepatocellular ballooning, varying degrees of steatosis, and lobular inflammation [25]. This progression is driven by several interrelated metabolic injuries, particularly insulin resistance and mitochondrial dysfunction, which impair β-oxidation and amplify DNL, subsequently causing the accumulation of toxic lipid metabolites in hepatocytes [52]. The lipotoxicity that results from the aforementioned promotes the production of ROS in excessive amounts, which causes damage to the membranes of mitochondria, activates stress-response signalling pathways, and induces oxidative stress [52,53]. The resulting cellular injuries stimulate the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), consequently exacerbating hepatic inflammation even further, as well as promoting the ballooning degeneration of hepatocytes, which are considered to be hallmarks of MASH pathology [53]. In PLWHIV, chronic ARV therapy further aggravates this process via drug-induced mitochondrial toxicity and dyslipidemia, which in turn aggravates oxidative stress and increases the inflammatory response [54]. However, even when pharmaceutical injuries are not applicable, metabolic stressors, such as obesity, insulin

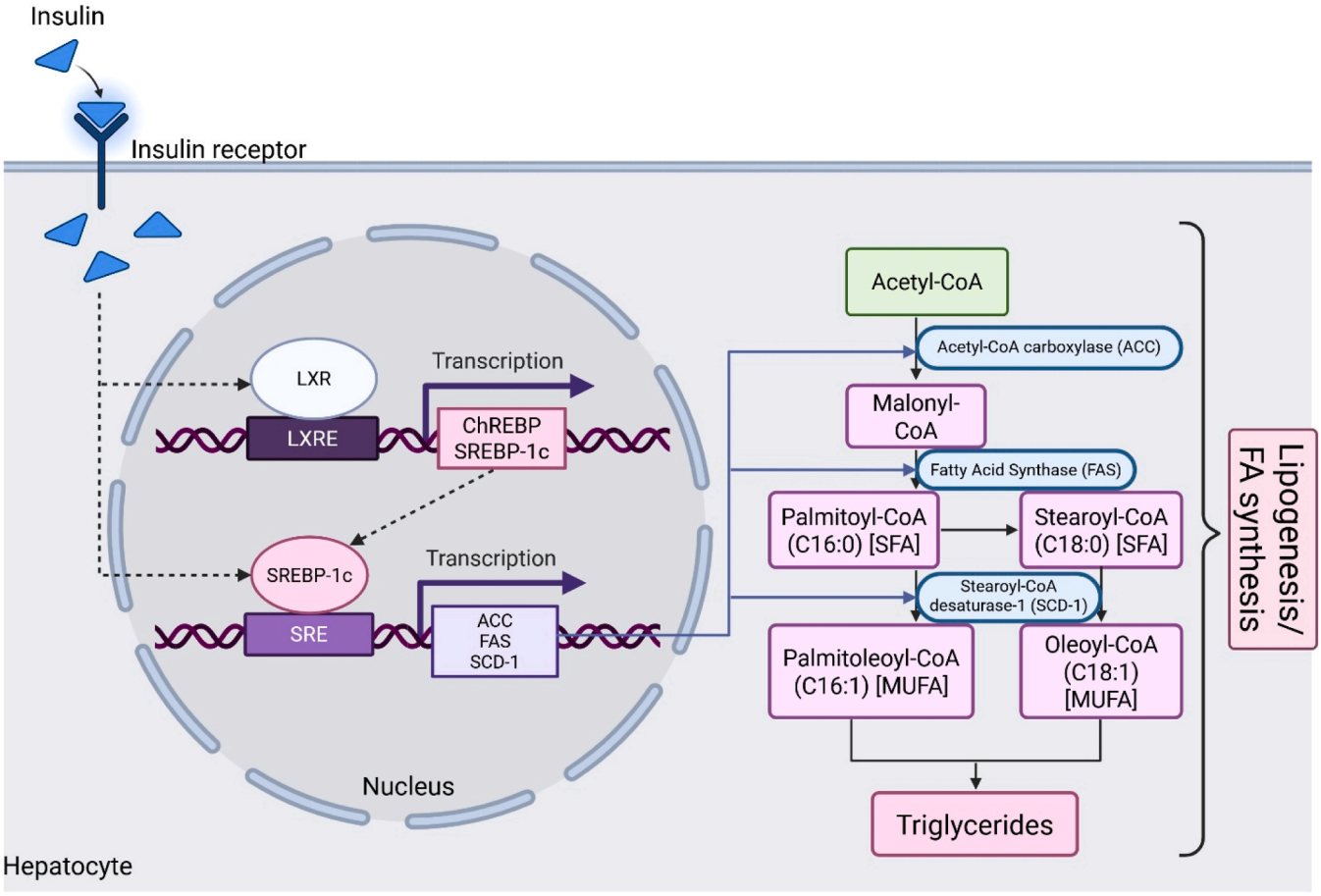

Fig. 4. The involvement of SREBP-1c in hepatic *de novo* lipogenesis.

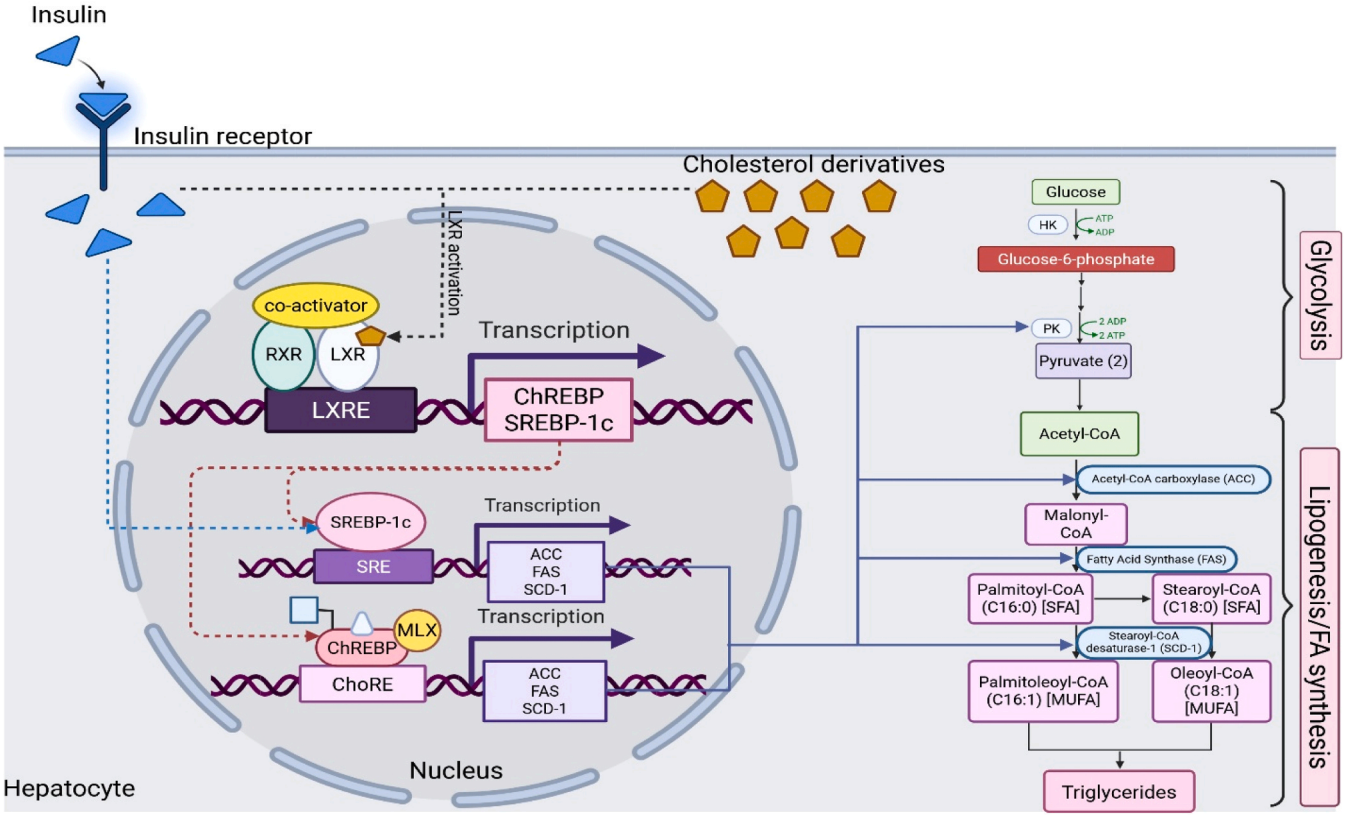

Fig. 5. Insulin and glucose stimulate transcription factors and control hepatic *de novo* lipogenesis [51]. .

resistance, as well as impaired adipokine signalling (reduced levels of adiponectin), can drive the progression from steatosis to MASH independently [25,53]. If no intervention occurs, this persistent hepatic inflammation and hepatocyte damage subsequently result in the activation of stellate cells, which release extracellular matrix proteins, thus creating a foundation for the accumulation of fibrotic tissue and the progression towards hepatic fibrosis [25,54]. In PLWHIV, mitochondrial toxicity induced by ARV therapy and systemic inflammation further exacerbates inflammation and hepatic injury, thereby accelerating the transition from steatosis to MASH [13,14,25,55]. When this condition is not addressed in a timely manner, this inflammatory environment fosters progressive fibrosis, which ultimately increases the risk of developing cirrhosis and hepatocellular carcinoma [26]. . Fig. 6

2.1.6. *Hepatic inflammation-driven fibrosis*

Hepatic fibrosis is a pathological response to prolonged hepatic injury, characterised by the accumulation of excessive extracellular matrix (ECM) components, including glycoproteins and collagen, which disrupt normal hepatic structure and function [56]. Within the broader framework of MASLD, fibrosis represents an advanced outcome of unresolved hepatic inflammation and is a pivotal indicator of the severity of the disease as well as its progression [56]. The fibrotic process is initiated during the transition from MASH, where chronic inflammatory signals (most notably IL-6 and TNF-α) and chronic oxidative stress stimulate hepatic stellate cells (HSCs), while other mesenchymal cells are activated and subsequently proliferate into myofibroblasts [56]. These are contractile cells that secrete abnormal ECM components, such as glycosaminoglycans and fibrillar collagens, which accumulate in the periportal and perisinusoidal regions of the liver, subsequently

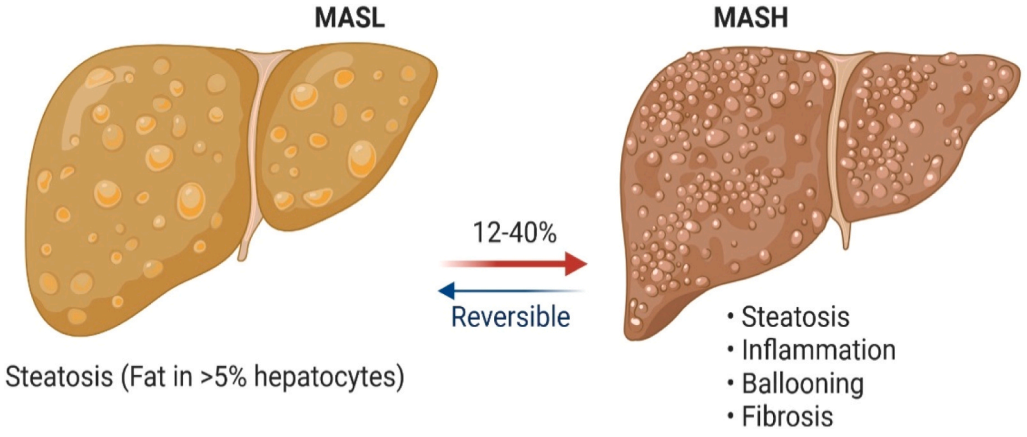

Fig. 6. The progression of MASLD pathogenesis, from MASL to MASH.

compromising sinusoidal blood flow and the viability of hepatocytes [56]. Additional factors that contribute to fibrotic remodelling include activated Kupffer cells, leukocytes, platelets, and damaged hepatocytes, which release profibrotic mediators that further amplify the activation of HSCs [56]. Although fibrosis is often clinically asymptomatic, the persistent progression thereof may result in structural distortion and increased intrahepatic vascular resistance, which can ultimately cause portal hypertension and provide the foundation for cirrhosis to develop [56]. Normal hepatic parenchyma cells are substituted with fibrous septa in cirrhosis, which leads to complications such as variceal haemorrhage, ascites, encephalopathy, and jaundice [56]. In the instance that the functioning of the liver becomes critically compromised, liver transplantation remains the definitive therapeutic intervention [57]. While liver biopsies are considered to be the diagnostic gold standard for assessing fibrosis, the growing use of non-invasive tools, like ultrasound, MRI, FibroScan, and biochemical markers (ALT/AST, FIB-4, ELF), is facilitating earlier detection and disease progression monitoring [58].

3. Current MASLD diagnostics methods

The diagnosis of MASLD necessitates an integrative approach, involving clinical assessment, laboratory biomarkers, and imaging methodologies that are designed to identify hepatic steatosis and evaluate the severity of the disease [58]. Increased levels of liver enzymes, particularly alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are common biomarkers, however, they lack specificity and they my present within normal limits during the early stages of the disease [58]. Newer blood-based biomarkers and scoring systems, including the Fibrosis-4 Index (FIB-4), the NAFLD Fibrosis Score, as well as the enhanced liver fibrosis (ELF) test, are progressively being employed as a non-invasive evaluation method to assess the extent of hepatic fibrosis [59]. Imaging techniques, such as ultrasound, facilitate preliminary screening for hepatic steatosis, whereas transient elastography (FibroScan) and magnetic resonance imaging-proton density fat fraction (MRI-PDFF) provide enhanced accuracy in quantifying hepatic fat content and stiffness, which are correlated with the progression of fibrosis [60]. Although computed tomography (CT) is sometimes utilized, this method exhibits reduced sensitivity for detecting early-stage steatosis [58]. Notwithstanding advancements in non-invasive diagnostic techniques, liver biopsy is still regarded as the gold standard for a definitive diagnosis, as well as the grading of steatosis, inflammation, and fibrosis [59]. Histological features like hepatocyte ballooning, which are enlarged hepatocytes with thin cytoplasm, are pivotal indicators of disease activity and constitute a fundamental component of MASH pathology [57]. These features are integral to the NAFLD Activity Score (NAS), which is a semi-quantitative metric utilized to evaluate disease severity and progression within both clinical and research frameworks [58]. However, certain limitations remain, as the NAS does not adequately reflect the presence or degree of fibrosis, and its interpretation may differ among pathologists [58]. Furthermore, numerous non-invasive methodologies are deficient in the precision needed to detect hepatocellular damage during the early or intermediate phases, thus posing a significant obstacle for timely therapeutic interventions [60]. Early detection through these diagnostic tests is pivotal for inferring therapeutic strategies, which include lifestyle alterations, pharmaceutical agents (such as metformin), and, in advanced cases of cirrhosis, liver transplantation [57].

4. Antiretrovirals and MASLD: exploring association and interactions

The first ARV agent, which formed part of the nucleoside reverse transcriptase inhibitor (NRTI) class, was approved for use in 1987. Since then, multiple ARVs, with various drug classes such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), have emerged. Some showed promising results in the treatment of HIV, while others had adverse effects, such as multiple resistance mutations. The search for an effective form of HIV treatment with reduced adverse effects is still ongoing [61]. Globally, about 39.0 million [33.1–45.7 million] people have been reported to be infected with HIV, of whom 76 % received ART in 2022 [62]. This relates to roughly 29.64 million people who utilised ART [62]. The African Region has shown 82 % antiretroviral therapy (ART) coverage among the population of approximately 25.6 million [21.6–30.0 million] people with HIV in 2022, relating to approximately 21.0 million HIV patients taking ART [62]. During the year 2023, approximately 75 % of people in the HIV infected population in South Africa were reported to be enrolled on ART [63]. Antiretroviral therapy (ART) is a combination treatment used to treat people who are infected with HIV, employing effective viral load suppression, immune function preservation or improvement, and lowering the chances of contracting cancers and opportunistic infections correlated with HIV [64]. This is accomplished via several modes of action, such as Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Integrase Inhibitors (INSTIs), Protease Inhibitors (PIs), Entry Inhibitors (EIs) [65]. There are various treatment regimens, or drug treatment plans, for ART, such as MTRs and FDCs. Multiple pill regimens, also known as “the cocktail”, entail taking a mixture of multiple pills during the day (every day), each pill being a distinct type of antiretroviral (ARV) drug/active ingredient [66]. While FDC regimens, also known as single-tablet treatment regimens (STRs), entail taking one tablet/capsule daily, each contains a mixture of various (2 or more) types (classes) of ARV drugs/active ingredients [66,67]. Fixed-dose combination ART has been shown to reduce treatment non-adherence due to the simplification of patient regimens [67]. The use of combination ART implies two NRTIs and an additional third potent agent [61]. There is a wide range of adverse effects associated with the use of ARVs, including diabetes mellitus and insulin resistance, dyslipidaemia, weight gain, and various hepatic effects [31]. Zidovudine (ZDV), an NRTI, as well as Lopinavir/Ritonavir (LPV/r), a PI, are associated with diabetes mellitus and insulin resistance [31]. Dyslipidaemia has been linked to the use of NRTIs (zidovudine, abacavir, tenofovir alafenamide), NNRTIs (efavirenz), PIs (ritonavir, lopinavir/ritonavir, darunavir and atazanavir/ritonavir), and INSTIs (elvitegravir/cobicistat), indicated by the increased levels of Low-density lipoprotein (LDL), High-density lipoprotein (HDL), and Triglycerides (TG) [31]. Hepatic effects are indicated with the use of NTRIs (zidovudine), NNTRIs (efavirenz and nevirapine), all PIs, INSTIs (dolutegravir), and EIs (maraviroc and fostemsavir). The development of severe liver flares in individuals with hepatitis B virus (HBV)/HIV coinfection is prevalent when NRTIs such as tenofovir alafenamide (TAF), tenofovir disoproxil fumarate (TDF), lamivudine (3TC), and emtricitabine (FTC) are used [31]. Efavirenz (EFV), an NNRTI, shows increased transaminases and the severe and sudden onset of hepatitis, while nevirapine (NVP), also an NNRTI, is associated with severe hepatotoxicity. These drugs are not to be used as post-exposure prophylaxis or given to individuals who have hepatic insufficiencies [31]. All PIs have been associated with hepatic decompensation and drug-induced hepatitis, and atazanavir (ATV) in particular causes indirect hyperbilirubinemia, leading to jaundice [31]. Dolutegravir (DTG), an INSTI, has shown association with hepatoxicity, while EIs such as maraviroc (MVC) and fostemsavir (FTR) have been shown to cause hepatoxicity and increased levels of bilirubin, respectively [31]. As for weight gain, INSTIs have been shown to increase weight gain more than the other ARV drug classes, but NRTIs, NNRTIs, and PIs have all shown an association with weight gain [31]. Both NTRIs and an NNRTI reduce HIV viral load by blocking HIV reverse transcriptase, which is an HIV enzyme that converts RNA to DNA, thus preventing HIV from replicating [68,69]. The benefits of using NRTIs and NNRTIs in combination are that they do not have overlapping sites of resistance or overlapping inhibition mechanisms. The main difference between NRTIs and NNRTIs is that NNRTIs do not require phosphorylation to be activated to carry out their inhibition mechanism [68]. Although these drug classes improve

the outcomes of HIV, they are associated with severe metabolic complications concerning insulin resistance, dyslipidaemia, and the subsequent development of MASLD onset [68]. Fig. 7 below demonstrates the mechanism of inhibition of HIV by NRTIs and NNRTIs. Fig. 8

4.1. Efavirenz and metabolic complications

Efavirenz (EFV) is an ARV medication used to treat and prevent HIV (prophylaxis), and has been FDA-approved [70]. The structure of EFV is 1,4-Dihydro-2H-3,1-benzoxazin-2-one substituted by chlorine at the sixth position and by trifluoromethyl and cyclopropylethynyl groups at the fourth position (Fig. 2) [71]. The compounds belonging to the NNRTI drug class varies from the NRTI drug class in that they do not poses a nucleoside structure, and thus do not rely on phosphorylation to exert their antiviral activity [72]. In combination with other antiretroviral agents such as emtricitabine and tenofovir, either as fixed dose or multiple pill regime, EFV can be used for prevention and management of HIV [70,73]. EFV is considered to be a first-generation NNRTI, which shows to be associated with multiple processes that play a role in the development of liver damage and hepatic steatosis [12]. The potential hepatotoxicity effects of efavirenz are correlated with transaminases serum concentration, a symptom of liver damage [70]. Furthermore, the NNRTIs are associated with lipodystrophy [70,73]. Lipodystrophy can be defined as a range of diversified disorders which are distinguished by the loss of body fat to various degrees [74]. Additionally, the predilection of developing insulin resistance along with the accompanying metabolic ramifications, such as hepatic steatosis, insulin resistance and hypertriglyceridemia are also involved in lipodystrophy [74]. In individuals with HIV, ART has been implicated as a contributor to drug-induced lipodystrophy, which is a common subtype of lipodystrophy [74]. It has been shown that efavirenz-based ART is associated with the progression of dysglycemia and dyslipidaemia, particularly total cholesterol elevation (HDL- and LDL cholesterol and TGs) [75]. Moreover, adipocytes have shown to contain quite a high concentration of EFV, which suppresses mitochondrial function, resulting in hepatic cell distress [12]. Consequentially, triglycerides (TGs) and fatty acids (FAs) accumulate in the hepatocyte cytoplasm [12]. This mitochondrial toxicity caused by EFV is suggested as a cause for the increase in BMI, despite the association with suppressed appetite [12]. Furthermore, LDL and HDL levels have also been shown to be increased in association with the use of EFV [31]. Lipohypertrophy has been observed with the use of EFV, but no causal relationship has been identified [31]. The risk of liver toxicity may be increased in comorbid conditions when EFV is used [30]. . Fig. 9

4.2. Emtricitabine and metabolic complications

Emtricitabine (FTC) is an NRTI used in conjunction with other ARVs to treat HIV by decreasing the viral load, as well as hepatitis B virus (HBV) [76]. Emtricitabine's chemical structure is 5-Fluoro-1-[2 R, 5S)-2-(hydroxymethyl)- [1,3]oxathiolane-5-yl]cytosine (FTC), which is similar to lamivudine's chemical structure and subsequently has a similar function (Fig. 3) [76,77]. In combination with tenofovir (300 mg), it is also used for pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) following potential HIV infection exposure [76]. In combination with tenofovir (300 mg) and efavirenz (600 mg), the formula exists as an FDC drug, which is given once a day orally as a treatment regimen for HIV [77]. The ARV drugs originating from the NRTI class, such as emtricitabine, result in a toxic interaction with mitochondrial DNA polymerase [76]. This acquired debilitation of the homeostasis of mitochondrial DNA in the liver can result in decreased ATP output and FA oxidation [78]. This subsequently leads to the development of hepatic abrasions, which include microvesicular steatosis and vast necrosis [78]. As a result, liver function is impaired and/or susceptibility to hepatic damage or injury can be elevated due to the resulting damage to hepatocytes caused by toxic agents [79]. Although unlikely, this toxic interaction is relevant to the development of liver steatosis, as well as myopathy, neuropathy, and lactic acidosis [76,77]. However, evidence suggesting that emtricitabine has a direct hepatotoxicity effect is very scarce, and has not been singled out as a direct contributor in cases of steatosis or hepatic failure [77]. A possible contributor to the discernible lack of substantial hepatotoxicity might be due to the minimal hepatic metabolism of emtricitabine (13 %) [77]. Additionally, it is not likely that the host mitochondrial or nuclear polymerases would use emtricitabine, on account that it is both restricted on the deoxyribose component at the 3' position and that it is an L-enantiomer of cytidine [77]. Thus, the hepatic effects of emtricitabine require further exploration. Table 1, Table 2

4.3. Tenofovir disoproxil fumarate and metabolic complications

Tenofovir is a nucleotide equivalent of adenosine 5'-monophosphate

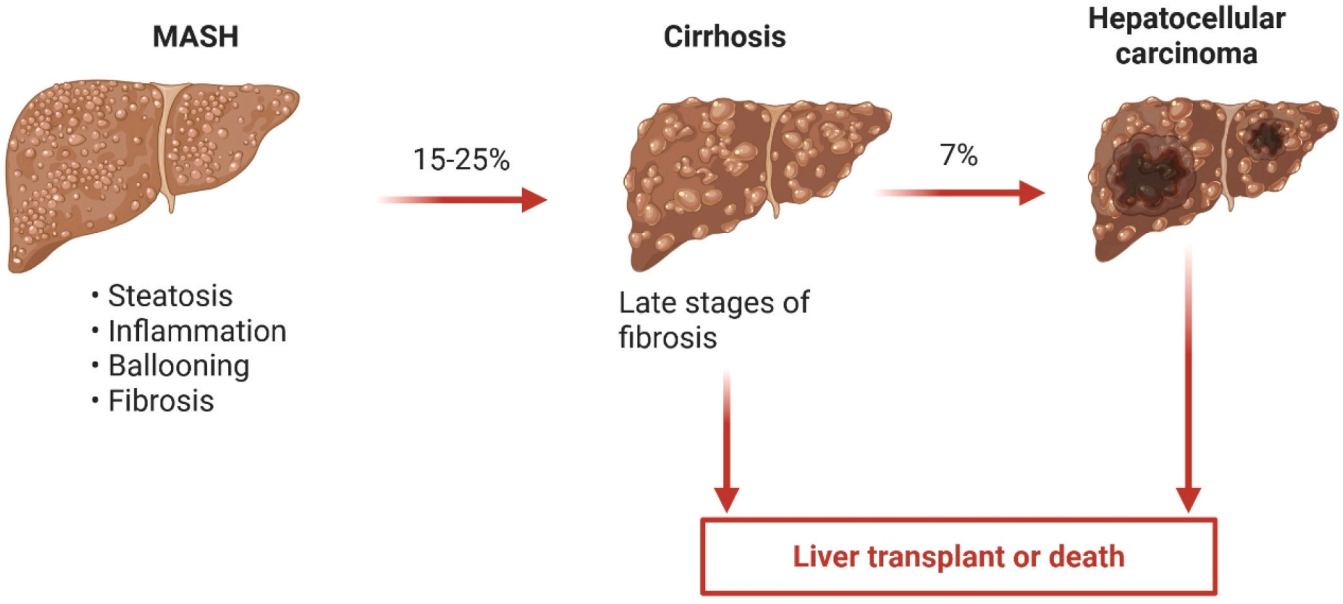

Fig. 7. The progression of MASLD pathogenesis, from MASH to cirrhosis and subsequently to hepatocellular carcinoma.

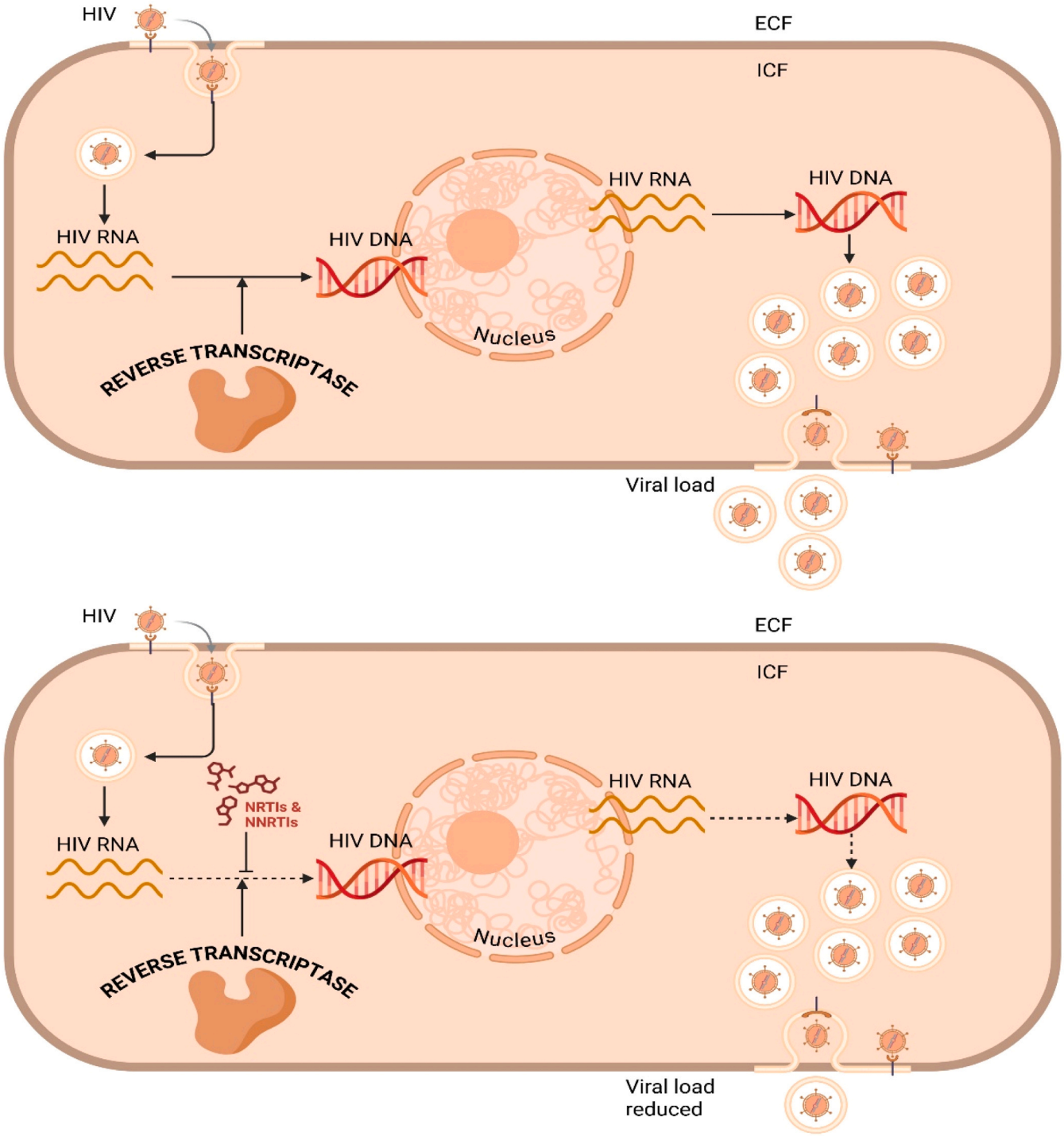

Fig. 8. NRTIs and NNRTIs inhibition mechanism for HIV.

that can counter HIV reverse transcriptase activity, which exhibits deficient oral bioavailability [80]. Tenofovir disoproxil fumarate (TDF) is a second-generation NRTI used in combination with other ARV agents as an FDA-approved prescription drug for the treatment of HIV [12]. This ARV is an ester prodrug of the NRTI tenofovir, meaning that this compound is broken down via metabolic processes inside the body, subsequently converted into a drug compound that is pharmacologically active with minimal or no pharmacological activity [81]. Prodrugs are designed to surmount pharmacodynamic and/or pharmacokinetic, as well as pharmaceutical challenges [81]. The purpose behind the synthesis of TDF was to improve oral absorption, as well as the cellular uptake of the ARV drug, to exert a more efficient therapeutic effect [80]. To execute its inhibitory effects against HIV reverse transcriptase activity, TDF needs to be converted to tenofovir diphosphate, which is the pharmacologically active metabolite [80]. This is achieved by hydrolysing TDF to tenofovir, followed by its phosphorylation via cellular kinases [80]. Tenofovir diphosphate competes for integration into the viral DNA with the nucleotide deoxyadenosine 5'-triphosphate, subsequently inhibiting HIV reverse transcriptase activity [80]. Upon the integration of tenofovir diphosphate into the viral DNA, the elongation of the DNA is discontinued due to the absence of a ribose ring [80]. The most frequent adverse effects of TDF include headaches, abdominal

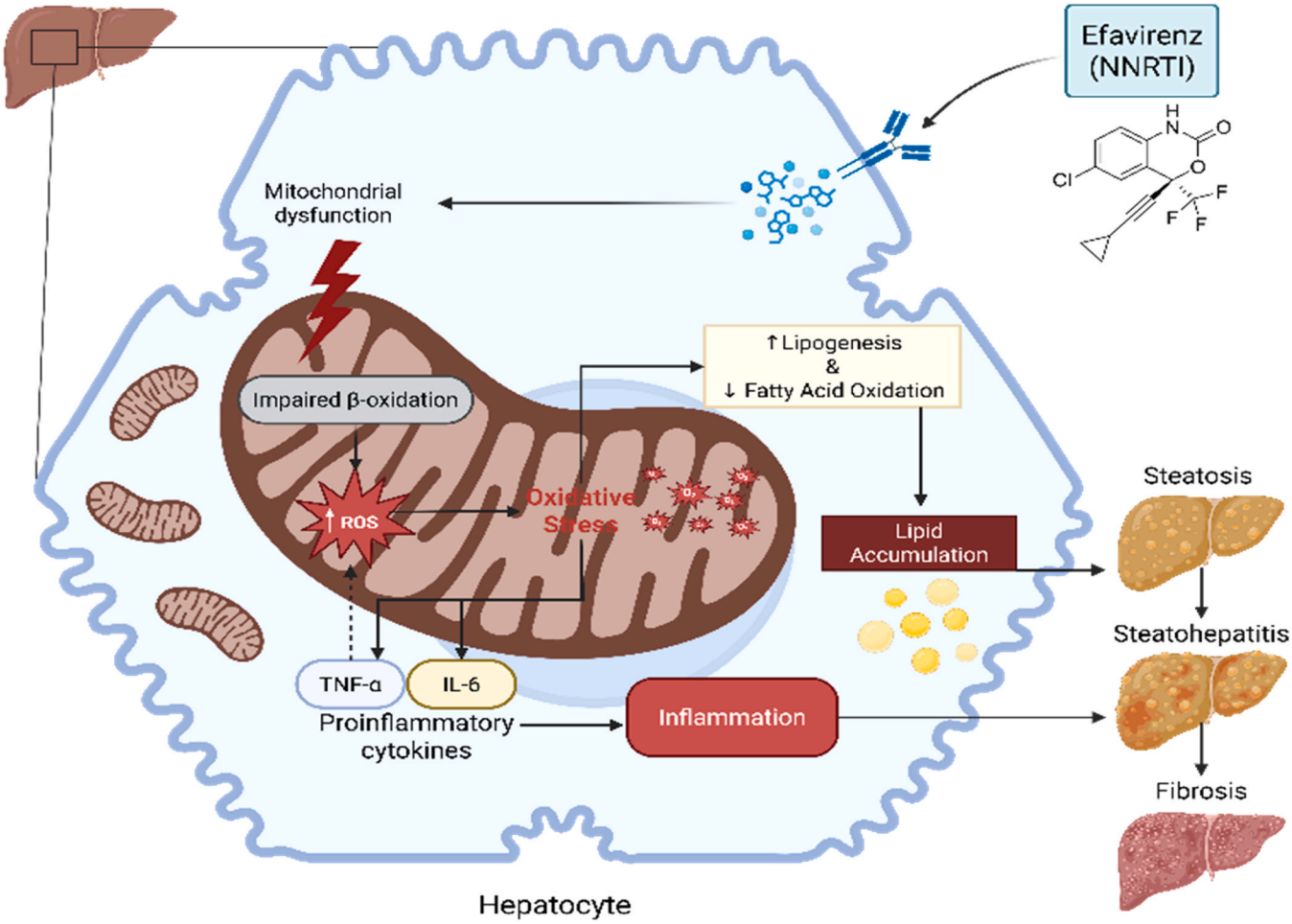

Fig. 9. Efavirenz mode of action leading to MASLD.

Table 1
ARV Classes and Hepatic Metabolic Effects.

Drug/ Compound	Class	Mechanism of Action	Hepatic Effect(s)	Combination Effects	Dose-Dependency	Statistical insights
Efavirenz (EFV)	NNRTI	Non-competitive HIV−1 reverse transcriptase inhibitor. Binds allosteric site.	Inhibition of Complex I&IV → Mitochondrial dysfunction →Activation of CYP450 enzyme → ↑ROS → Oxidative Stress →↓Fatty Acid Oxidation & SREBP−1c and ChREBP activation → ↓FA breakdown & ↑ Lipogenesis → Lipid Accumulation → Steatosis	In combination with TDF or FTC, results in an increase in hepatic lipid accumulation, and elevated levels of ALT/AST liver enzymes can be observed [82].	In-vitro dose-response mitochondrial toxicity detected at ≥ 10 μM.	The use of ARV therapy that contain EFV is associated with up to 50 % prevalence of MASLD amongst PLWHIV. Switching off of EFV has shown to reduce hepatic fat in small clinical studies [83,84].
Emtricitabine (FTC)	NRTI	Cytidine analogue – competes with natural nucleosides to terminate synthesis of viral DNA.	DNA polymerase inhibition → mtDNA depletion → ↑ROS → Oxidative Stress → ↓ Fatty Acid oxidation → Lipid Accumulation → Steatosis	Co-administration with EFV results in enhanced mitochondrial toxicity and subsequently increased hepatic stress and damage [82].	Monotherapy indicated no significant alterations in hepatic lipid profile. Mitochondrial dysfunction is only induced at very high, physiologically non-viable concentrations and is thus not considered clinically relevant.	All NRTIs, including FTC and others, have shown minimal association with MASLD when administered alone. In combination regimens, however, ~40–50 % of PLWHIV have MASLD [83,85].
Tenofovir disoproxil fumarate (TDF)	NRTI	Adenosine analogue – results in viral DNA chain termination	DNA polymerase inhibition → mtDNA depletion → ↑ROS → Oxidative Stress → ↓ Fatty Acid oxidation → Lipid Accumulation → Steatosis	Co-administration with EFV results in the mutual stimulation of ROS production, subsequently elevating the levels of liver enzymes [82].	Mild dose-response mitochondrial toxicity is only seen at high concentrations, while the therapeutic plasma concentrations do not generally impair mitochondrial function.	The prevalence of MASLD among PLWHIV on TDF-inclusive regimens also approaches ~40–50 % with ~15 % having advanced fibrosis [83,85].

Table 2
Emerging treatment strategies for MASLD in PLWHIV.

Therapeutic Intervention	Clinical Use	Status	Mechanism of Action	Hepatic Benefit in MASLD	Relevance to PLWHIV
GLP−1 agonists	T2DM (antidiabetic) and obesity (incretin mimetics)	Currently in phase III clinical trials for MASLD treatment.	• ↑ insulin sensitivity • ↑ β-oxidation • ↓ lipogenesis • ↓ appetite	• Possible anti-fibrotic effect • ↓ hepatic lipid accumulation (steatosis) • ↓ liver enzymes ALT/AST [91,92]	Provides a promising outlook for PLWHIV who are ARV users with co-morbidities such as T2DM and/or obesity [91,92]
Resmetirom (MGL−3196)	Thyroid hormone receptor (THR)-β agonist	Currently in phase III clinical trials for MASLD treatment.	• ↓ mitochondrial toxicity • ↑ lipid metabolism • ↓ hepatic lipid accumulation	• ↓ hepatic steatosis • ↓ fibrotic biomarkers • More favourable lipid profile [90].	Suitable for HIV patients presenting with ARV-related steatosis and dyslipidemia [90]
Metformin	T2DM (antidiabetic)	Mainly recommended for T2DM, and not often recommended for MASLD alone.	• ↑ AMPK activity • ↓ hepatic gluconeogenesis • ↓ *de novo* lipogenesis	• Does not demonstrate significant effect on fibrosis. • Exhibits modest liver ft reducing effects [93]	Deemed as safe to use for T2DM in PLWHIV and does not show a significant benefit on liver histology [93].

pain, nausea, vomiting, diarrhoea, anorexia, asthenia, and flatulence [80]. Compared to first-generation NRTIs, such as zalcitabine, TDF has been reported to have an improved adverse effects profile, including the lipid profile [12]. Serum lipids do not seem to be affected by TDF; however, an increase in serum lipid levels (TGs, LDL, and HDL) is observed when switched from TDF to tenofovir alafenamide (TAF) [12]. Equivalently, those same lipid parameters are decreased when switching back to TDF, hence the risk of dyslipidaemia is reduced [12,31]. Fig. 10

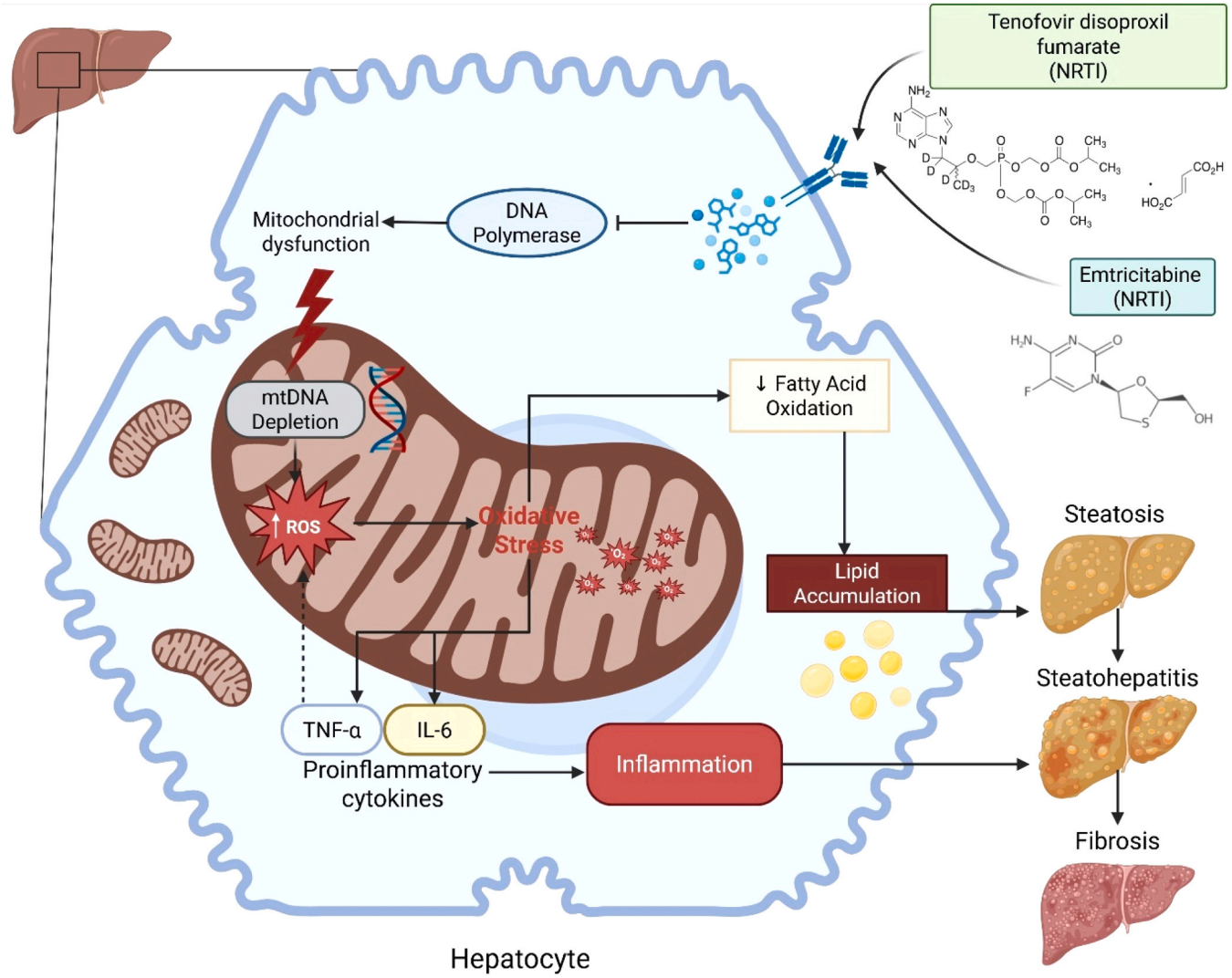

Fig. 10. Emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) mode of action leading to MASLD.

5. HIV-ART -de novo lipogenesis-MASLD interaction

Previous publications regarding the topic have indicated that both the SREBP-1c and ChREBP transcription factors are pivotal for the synchronised and maximised induction of lipogenesis and glycolysis in response to excess carbohydrate levels [40,41,45]. Moreover, ChREBP is crucial for the basal and carbohydrate-induced expression of glycolytic genes, whereas SREBP-1c is not [40,41,45]. However, both factors are required for the complete initiation of the hepatic lipogenic pathway via glucose and insulin, which highlights the distinct yet overlapping roles of these transcription factors [40,41,45]. They are also mutually regulated, which is supported by the direct regulation of SREBP-1c by ChREBP [40,41,45]. It is postulated that the binding of ChREBP to ChoRE motifs in the SREBP-1c promoter mediates the hepatic reduction in the levels of SREBP-1c mRNA and nuclear SREBP-1c protein when ChREBP is eliminated from the liver [40,41,45]. Contrarily, ChREBP cannot mediate the sucrose-induced lipogenic response without SREBP activity, as demonstrated by the lack of lipogenic gene expression restoration in SREBP-deficient mouse models by ChREBP overexpression [40,41,45] This interplay between these transcription factors ensures that hepatic fatty acid production occurs only when both carbohydrates (acting via ChREBP) and insulin (acting via SREBP-1c) are present [40, 41,45]. In addition, LXR is also involved, as supported by the necessity thereof for the basal expression and the transcriptional expression of SREBP-1c via insulin [40,41,45]. It has also been shown to directly activate ChREBP and some lipogenic genes [40,41,45]. This ultimately creates a complex network where LXR activity is also influenced by the production of sterol ligands via SREBP-2, which in turn affects the expression of SREBP-1c and ChREBP [40,41,45].

6. Potential MASLD therapeutic interventions

6.1. Glucagon-like peptide-1 receptor agonist (GLP-1 RAs)

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) represent a category of incretin-based pharmacotherapies that have been specifically developed for the management of T2DM [86–88]. These pharmacological agents mimic the physiological actions of endogenous GLP-1, thereby elevating glucose-dependent insulin secretion while suppressing the release of glucagon, slowing down gastric emptying and promoting a sense of satiety [86–88]. Commonly used GLP-1 RAs include liraglutide, semaglutide, and dulaglutide, with emerging formulations now targeting multiple receptors, such as GIP and glucagon [86–88]. The hepatoprotective profiles of these agents have been studied and are showing an increasing interest in their potential repurposing for the management of MASLD [86–88]. GLP-1 RAs have various therapeutic benefits for metabolic pathologies, including T2DM and obesity, thus serving as a pivotal parallel intervention for MASLD [86–88]. The mechanisms by which GLP-1 RAs elicit their primary function, which is the induction of significant weight loss via appetite suppression and deceleration of gastric emptying, are of particular interest as a direct beneficial impact on MASLD, considering that weight loss of 7–10 % is regarded as one of the therapeutic majors for the MASLD condition [86, 88]. In addition, GLP-1 Ras have been shown to improve systemic insulin sensitivity and glycaemic control, which are cardinal to the progression of MASLD [86–88]. Furthermore, GLP-1 RAs also improve liver functions as evident through the liver function biomarkers, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT).These biomarkers are also indicative of steatosis-induced hepatocellular inflammation and injury [86–88]. Previous studies have demonstrated that GLP-1 RAs, like semaglutide and liraglutide, resolve steatohepatitis histologically in a considerable number of patients [86,88] Even though the direct effect of GLP-1 RAs on pre-existing hepatic fibrosis regression is still unknown, these agents have been demonstrated to reduce and/or slow down hepatic fibrosis progression [86,88]. The underlying mechanisms contributing to these hepatic benefits are theorised to be multifactorial in nature, integrating both the indirect effects of weight loss and enhanced metabolic parameters, as well as potential direct interactions with the liver through the improvement of hepatic insulin resistance, elevation of adiponectin levels, modulating lipid metabolism pathways, and mitigating hepatocyte apoptosis and systemic inflammation [86–88]. Moreover, newer dual and triple agonists (targeting GLP-1, glucagon receptors, and/or GIP), such as tirzepatide, are demonstrating superior efficacy in weight loss, glycaemic regulation, and hepatic fat reduction, thus suggesting promising future strategies for the management of MASLD [86,88]. Thus, GLP-1 RAs are progressively being recommended for MASLD patients presenting with concomitant T2DM or obesity due to their comprehensive cardiometabolic benefits and hepatoprotective properties [86,87].

6.2. Thyroid hormone receptor-beta (THR-β) agonist

Resmetirom, commercially known as Rezdiffra, represents a revolutionary oral thyroid hormone receptor-beta (THR-β) agonist pharmacotherapeutic approach for patients diagnosed with non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) accompanied by moderate to severe hepatic fibrosis (stages F2-F3) [89]. This agent is explicitly recommended as an adjunct to dietary and exercise interventions [89]. The pharmaceutical mechanism of Resmetirom involves the selective activation of the thyroid hormone receptor-beta (THR-β), which is the predominant variant of thyroid hormone receptor found in hepatic tissue [89,90]. This selective receptor activation results in a decrease in intrahepatic triglycerides, enhances fatty acid oxidation, and promotes mitochondrial biogenesis, consequently reducing the lipotoxicity in the liver [89]. The medication also contributed to improved liver histology, resolution of MASH without fibrosis progression, and continuous lipid profile improvements, including considerable reductions in LDL-C, triglycerides, and apolipoprotein B (apo B) [89,90]. This dual advantage serves to reinforce both hepatic health and the reduction of cardiovascular risk [89,90]. Although generally well tolerated, Resmetirom as exhibited common adverse effects, including gastrointestinal disturbances such as nausea, diarrhoea, constipation and vomiting [89,90]. Additionally, a slightly increased incidence of gallstone-related complications has been observed, although the overall occurrence rates remain low (less than 1 per 100 persons per year) [89]. Resmetirom is contraindicated in individuals with decompensated cirrhosis, and additional longitudinal studies are required to fully ascertain its safety, effectiveness, and its definitive role in the prevention of advanced hepatic conditions such as cirrhosis or hepatocellular carcinoma [89,90].

7. Implications for clinical practice

The previous reports suggest that approximately 18 % of the individuals utilising ARV treatment develop drug-induced liver injury (DILI) as a consequence [94]. It is especially difficult to identify the prospective hepatotoxic effects of each drug when the ARV is a fixed-dose combination [94]. All ARVs may promote hepatotoxicity; however, it has been theorised that NRTIs are the most probable perpetrator [94]. Any acute or chronic hepatobiliary state could imitate DILI. In addition, there are no particular diagnostic tests available; thus, this hepatotoxicity is clinically formidable to diagnose [95]. Nevertheless, taking the individual's history of known drugs and overall patient history into account, as to potentially identify and exclude any underlying or pre-existing liver disease, is the first step to achieving a diagnosis [95]. Methods such as histological testing, which includes testing for abnormalities in alanine aminotransaminase (ALT), alkaline phosphatase (ALP), aspartate transferase (AST), gamma-glutamyl transpeptidase (GGT), albumin, prothrombin time (PT), and total bilirubin can be used to diagnose and differentiate between the various types of hepatic injury [95]. The elevation of transaminases (e.g., ALT) by

approximately 3 times the upper limit of normal (ULN) compared to the ALP level is a marker for hepatocellular injury [95]. Dysregulated liver function is indicated by observed coagulopathy in ALF [95]. Moreover, imaging methods, such as MRI and an abdominal ultrasound, is used to aid with the diagnosis of DILI, whereas invasive procedures such as a liver biopsies is not required for diagnosis, but could be helpful in exclusion if/when it is suspected that there are other unrelated sources of hepatic disease [95]. Generally, the primary treatment for DILI is the cessation of the offending agent, followed by close monitoring for resolution [94]. The manifestation of DILI can be exhibited in various clinical phenotypes, such as drug-induced steatohepatitis (DISH) and drug-induced steatosis (DIS) [96]. These types of DILI are characterised by fat deposits in hepatocytes, and more severe cases thereof are associated with prolonged use of the hepatotoxic agent and hepatic drug accumulation [96]. Many drugs, including ARVs, are pathogenic factors of hepatic steatosis [96]. The drugs that can induce steatosis have been divided into three groups by some authors [1]: drugs that cause metabolic changes including weight increase, dyslipidaemia, and insulin resistance (e.g. glucocorticoids, certain ARV classes) [2], drugs that independently cause steatosis (e.g. amiodarone) and [3] drugs that cause steatosis periodically (e.g. carbamazepine) [96]. As previously stated, NRTIs have been frequently associated with hepatic damage mirroring steatosis, since they cause impaired hepatic FA oxidation as the result of defective mitochondrial DNA replication, and thus defective mitochondrial function [96]. Although NRTIs are well established in the development of MASLD, it has proven to be difficult to determine the exact role they play therein, as patients might have had exposure to more than just one [96]. Seen as ARV usage is a known risk factor contributing to the development of DILI and its various clinical phenotypes, but cannot be ceased, it is recommended that prospective ARV users should be screened for pre-existing or underlying liver conditions, such as MASLD, prior to treatment initiation [97]. This is done employing diagnostic testing using liver histology, which should be repeated six weeks after treatment initiation and done routinely throughout the course of treatment [98]. This is done to effectively combat/manage any potential liver damage caused by the chronic use of ARVs [98]. Although DILI and hepatic steatosis are quite commonly associated with the use of ARVs, there are recommended ways to mitigate/minimise their adverse hepatic effects. These include determining the individual's predisposition for developing liver disease by identifying possible genetic, immunological, and biological markers, considering the individual's age [98]. With regards to alcohol consumption, in addition to having been shown to reduce treatment adherence and counteract medicinal effects, alcohol in itself also causes severe hepatic complications [99,100]. Therefore, an individual's level of alcohol consumption should also be taken into account and advised to cease the usage thereof during treatment [99]. Moreover, implementing interventions such as a healthy diet, an exercise plan, and smoking cessation to limit hepatic lipid accumulation can be beneficial [101]. In addition to the previously mentioned non-pharmaceutical methods, there are multiple pharmaceutical treatment approaches available, which include the use of oral glucocorticoids (GCs), such as prednisone, to suppress unrestricted inflammatory activity [102]. However, hyperglycaemia has been identified as an adverse effect associated with the use of GCs [103]. To combat this, metformin is co-administered, which has a beneficial effect on glycaemic balance [103]. Furthermore, metformin hinders cirrhosis progression by modulating hepatic stellate cells' (HSCs) proliferation and activation [104]. Some studies have indicated that metformin governs lipid metabolism as a result of its ability to activate AMPK via affected ATP/AMP ratios, which is of great interest in MASLD [104]. Although metformin is mainly used to treat hyperglycaemia in T2DM, it has also been shown to protect against hepatotoxic drugs that cause chemical- and drug-induced liver injury (DILI) [104].

8. Conclusion and authors' perspectives

Metabolic dysfunction-associated steatotic liver disease is a condition that involves the build-up of excess fat in the liver that is not due to the excessive use of alcohol and shows a significant prevalence among PLWH. Obesity and T2DM have been identified as conditions that play a significant role in the development of MASLD onset, as can be seen by the prevalence thereof. The lack of physical activity, an unhealthy diet (high-fat diet), certain medications like ARVs, and conditions like obesity, are all known to cause hepatic insulin resistance by activating PKCε, which binds to the insulin receptors and impairs their function. This subsequently reduces insulin receptor substrate-2 (IRS-2) activity, which reduces hepatic glucose uptake via GLUT-2, and glucose synthesis persists unabated. Hepatic Insulin Resistance, due to impaired insulin receptor function, is narrowly associated with hepatic lipid accumulation and the development of MASLD. The aetiology of hepatic lipid accumulation, also known as steatosis, includes a sedentary lifestyle, an unhealthy high-fat diet, certain medications such as ARVs, as well as conditions such as obesity & T2DM, which are all known to cause dyslipidaemia. Hepatic lipohypertrophy occurs due to the combined effects of increased fatty acid (FA) oxidation, lipogenesis, and lipolysis, as well as impaired lipid export. Sterol Regulatory Element Binding Proteins (SREBPs) are responsible for the expression of several enzymes necessary for FA and Triglyceride synthesis, which ultimately activate lipid synthesis. Hepatic lipid accumulation results in the development of MASLD due to the resulting excessive fat deposits and the associated complications thereof. The HIV viral load is suppressed by FDC-ART, which reduces the chances of death and/or opportunistic infections because of a weak immune system, by enabling improved immune function preservation. This is accomplished via several modes of action of the ARV drug classes. Although these drug classes improve the outcomes of HIV, they are associated with severe metabolic complications concerning insulin resistance, dyslipidaemia, and the subsequent development of MASLD onset. Another established risk factor contributing to MASLD is ARVs, because they have been shown to induce insulin resistance and dyslipidaemia, which are the precursors to MASLD onset. As the global HIV cases grow annually, so does the distribution and administration of ARVs due to the increased demand. Therefore, the increased MASLD prevalence and occurrence in PLWH could be attributed to the use of ARVs. However, the mechanisms behind how ARVs result in metabolic dysfunction and subsequent MASLD development have not entirely been established and addressed for the massive numbers of HIV infected individuals who are on fixed-dose combination ART [5].

Recommendations and future directions

Considering that the prevalence of MASLD among PLWHIV is an ever-evolving global burden, the demand for novel, combined, and/or proactive approaches grows more dire in the effort to alleviate the hepatic adverse effects associated with the use of chronic ART. We therefore propose clinical strategies that incorporate pre-treatment hepatic screening protocols using non-invasive imaging methods, such as FibroScan, and liver enzyme testing before initiating ART in order to evaluate the baseline condition of the liver, especially in patients presenting with T2DM, obesity, or metabolic syndrome. Biomarker-based screening by means of traditional liver function testing for serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), bilirubin, and alkaline phosphatase (ALP), as well as fibrosis scores, should be integrated into these protocols in order to serve as early biological indicators of liver injury, and long-term MASLD progression monitoring in PLWHIV. Additionally, we propose the inclusion of GLP-1 receptor agonists in treatment strategies for PLWHIV with concomitant insulin resistance, obesity, or hepatic steatosis, given that they play a dual role in hepatic protection and metabolic regulation. Moreover, it is encouraged that ARV regimens

with traditional hepatotoxic combinations should be replaced with ARV regimens that exhibit a reduced hepatic and metabolic toxicity profile, where clinically feasible, especially in high-risk patients. Advances in personalized medicine in HIV care are desired by means of lipidomic, genomic, and metabolic profiling with the aim to provide tailored ARV regimens based on a patient's hepatic risk profile and response to treatment. Furthermore, current and future clinical studies should assess the long-term hepatic outcomes of new ARV medications, as well as their interactions with liver-protective agents, like Resmetirom. The incorporation of routine hepatological evaluation into HIV clinical care practices is pivotal to improve longitudinal outcomes and diminish MASLD-related morbidity in this vulnerable population.

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CRediT authorship contribution statement

Mlindeli Gamede: Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Marilize Horn:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Nontobeko Gumede:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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