Causes and outcomes of hepatic fibrosis in persons living with HIV

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Purpose of review
The epidemiology of liver disease in people living with HIV has evolved since the arrival of effective hepatitis C virus (HCV) treatment. Nonalcoholic fatty liver disease (NAFLD) in HIV patients is highly prevalent while hepatitis D, hepatitis E, and occult hepatitis B remain underappreciated. We discuss mechanisms of fibrosis in HIV and review clinical outcomes of HIV-associated liver diseases.

Recent findings
HIV-HCV co-infection is receding as a cause of progressive liver disease, but fibrosis biomarkers after HCV treatment remain elevated. Antiretroviral therapy (ART) with anti-hepatitis B virus (HBV) activity promotes stable liver disease, but oversimplifying ART regimens in unrecognized suppressed HBV may lead to activation of HBV. A high prevalence of fibrosis and rapid progression of fibrosis are seen in HIV-associated NAFLD, with visceral fat as a major risk factor. Newer ART such as integrase strand inhibitors may have limited intrinsic hepatoxicity but do increase weight, which may secondarily lead to hepatic steatosis. Promising therapies for HIV-associated NAFLD include tesamorelin and CCR5 blockade agents.

Summary
Our understanding of the natural history and pathogenesis of liver diseases in HIV has advanced and adapted to the changing landscape of liver disease in this population. Future research should evaluate long-term clinical and histological outcomes, prevention strategies, and treatment options to improve morbidity and mortality in HIV-related liver diseases.

Keywords
antiretroviral therapy, HIV, liver fibrosis, nonalcoholic fatty liver disease, viral hepatitis

INTRODUCTION

With the introduction of effective combination antiretroviral therapy (cART) in 1996, the lifespan of people living with HIV infection (PLWH) was extended. Longer life expectancy led to shifts in the causes of morbidity and mortality in individuals with HIV infection, and chronic liver disease has emerged as the second leading cause of non-HIV related mortality [1].

In the early 2000s, concern centered on the impact of HIV-hepatitis C virus (HCV) co-infection on the acceleration of liver disease progression. However, the field has continued to evolve in the last decade. Due to the advent of direct-acting antiviral (DAA) agents in 2011, HCV treatment has become safe and effective for HIV patients and has corresponded to improvement in clinical outcomes. Now, attention has moved towards other etiologies of liver disease, such as the high prevalence of HIV-associated nonalcoholic fatty liver disease (NAFLD), increased recognition of hepatitis delta virus (HDV) and hepatitis E virus (HEV), particularly in Europe, and the continued contribution of hepatitis B virus (HBV) to liver injury and mortality in co-infected patients despite widespread HBV suppression by dual-acting agents used in cART.

In this article, we will examine unique profibrogenic pathways potentiated by HIV and HIV-associated liver diseases, the impact of antiretroviral therapy on liver fibrosis, and emerging therapies that may modify outcomes of liver disease in PLWH.

UNIQUE MECHANISMS OF FIBROSIS IN HIV

Hepatic fibrosis results from acute or chronic liver injury and is a normal wound-healing response that

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KEY POINTS

- Fibrogenic pathways from HIV include direct effects on liver cells, immune activation from bacterial translocation, and altered immunity from T-cell exhaustion and death.
- Although hepatitis C co-infection has declined, hepatitis B and hepatitis D are still main contributors to HIV-related liver disease, and hepatitis E is particularly common in Europe.
- Nonalcoholic fatty liver disease is highly prevalent in people with HIV and is associated with rapid fibrosis progression, with visceral fat related to lipodystrophy as a clinical predictor.
- Despite lowered risk of fibrosis progression with effective antiretroviral therapy, mechanisms of fibrogenesis are not completely reduced, and further studies in the possible contribution of contemporary antiretroviral therapy to fatty liver disease are needed.
- Emerging therapies include CCR5 inhibitors for modulation of hepatic fibrosis, tesamorelin for HIV-associated nonalcoholic fatty liver disease, and bulevirtide and lonafarnib as potential cures for hepatitis D.

leads to increased deposition of extracellular matrix (ECM) composed of fibrogenic type I and III collagen [2]. Hepatic stellate cells (HSC) are key effector cells that are activated to collagen type I-producing myofibroblasts in response to liver injury. Other immune and parenchymal cells, such as hepatocytes, macrophages, and natural killer cells, produce various extracellular signals to regulate activation of HSCs. Through pathways that cause HSC apoptosis, senescence, or quiescence, cessation of liver injury leads to either resolution of fibrosis or remodeling of deposited matrix with subsequent decrease in fibrosis stage [3]. However, repeated and chronic liver injury from a multitude of etiologies, such as viral infections, alcohol, and metabolic syndrome causes fibrosis progression through continued activation of profibrogenic pathways. These pathways promote increased synthesis and deposition of type 1 collagen and HSC survival, ultimately propagating large amounts of scar formation and leading to the development of cirrhosis and decompensated liver disease. This process may take decades, and the insidious nature of progression often lulls clinicians into a false sense of security in their patients' health status.

Direct HIV and HIV-related effects

HIV infection itself promotes fibrogenesis through a variety of mechanisms. These include direct effects on hepatocytes, stellate cells, and Kupffer cells, immune activation from increased bacterial translocation into portal blood, and immune system dysregulation through depletion and death of T-cells (Fig. 1).

HIV can enter hepatocytes, but data are controversial with regards to its capacity for productive infection [4]. However, HIV envelope proteins interact with the HIV coreceptors CC-motif chemokine receptor 5 (CCR5) and C-X-C motif chemokine receptor 4 (CXCR4) expressed on hepatocytes. This promotes reactive oxygen species (ROS) accumulation and transforming growth factor beta-1 (TGFβ1) signaling, which stimulate HSCs to produce ECM through upregulation of genes collagen type 1 α 1 (CoL1A1) and TIMP metallopeptidase inhibitor 1 (TIMP1). Studies by Chung and colleagues on HIV-HCV co-infection in co-culture of hepatocytes (Huh7.5.1 cells) and HSCs (LX2) demonstrated that HIV and HCV independently and cooperatively activate these profibrogenic effects [5,6]. In addition, HIV-induced apoptosis of hepatocytes and subsequent phagocytosis by macrophages and HSCs also contribute to fibrosis [7,8].

HIV can directly infect HSCs and hepatic macrophages (Kupffer cells). HIV activation of HSCs, through CCR5 dependent and independent pathways, stimulates production of ECM [9,10]. Kupffer cell activation by HIV through stimulation of toll-like receptors (TLRs) promotes proinflammatory cytokines and ECM production by HSCs [11,12]. This process is represented by the release of soluble CD163 (sCD163), which is a macrophage activation marker. sCD163 levels are elevated in both HIV and HCV infection, with highest levels in HIV-HCV co-infection, and are significantly associated with development of hepatic fibrosis [13,14].

Liver fibrogenesis may also be propagated by immune activation from HIV-associated microbial translocation [15]. Early and severe depletion of CD4 T-cells in the gastrointestinal tract leads to a breach in the intestinal immune barrier through enterocyte apoptosis and tight junction disruption, as well as gut dysbiosis [16–18]. Bacterial translocation results in endotoxins such as lipopolysaccharide (LPS) in the portal circulation, which are then drained through the liver until later stages of hepatic fibrosis lead to shunting. This process may contribute to activation of proinflammatory and profibrogenic pathways. LPS is elevated in HIV infection [19] and has been shown to activate HSCs and macrophages through interaction with TLRs [20].

In patients with HCV or HBV-induced chronic liver disease, altered immunity in HIV infection can also accelerate fibrosis progression. In a study of HIV-HCV co-infected patients, co-infection was associated with lack of critical CD4 T-cell responses to HCV

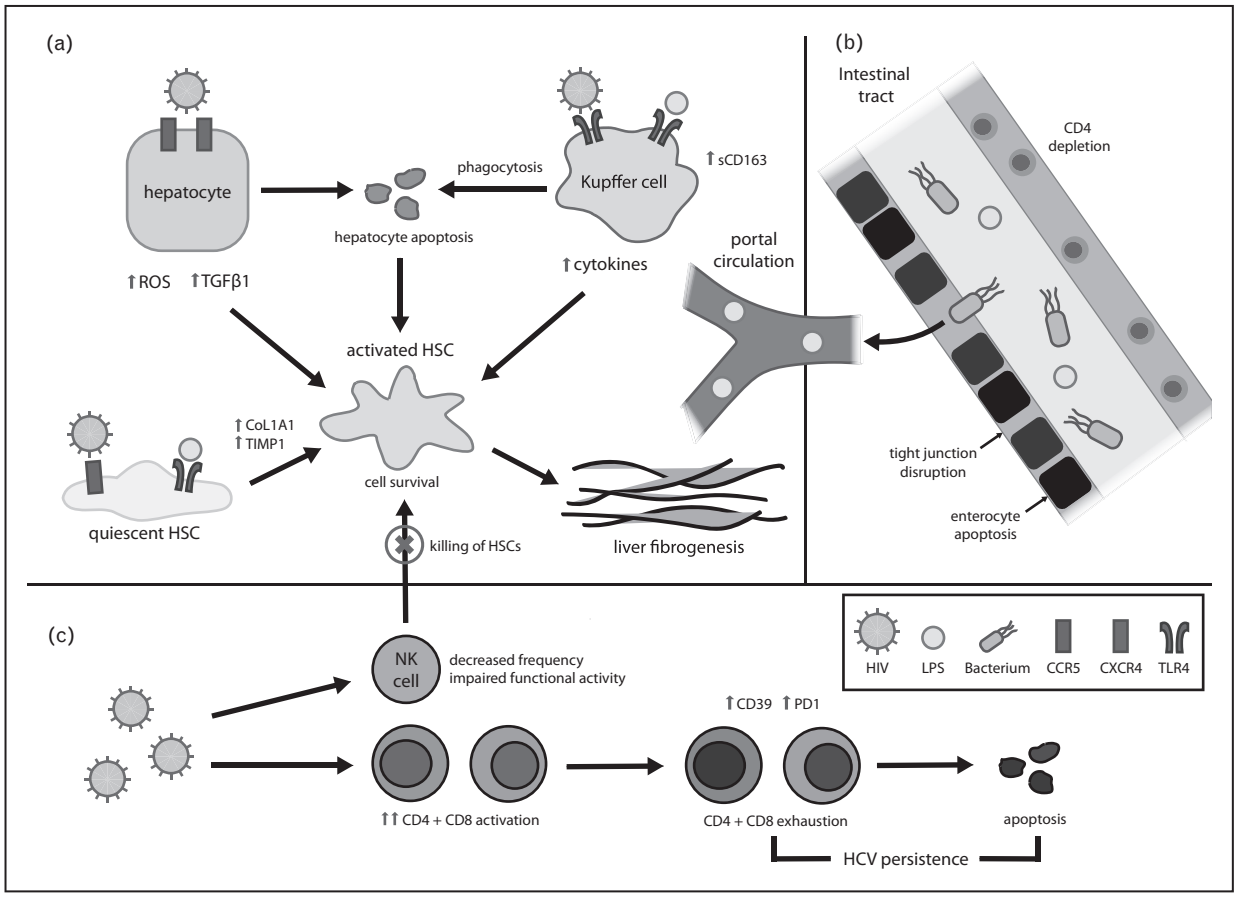

FIGURE 1. a. Direct HIV Effects. HIV interacts with hepatocytes through HIV co-receptors CCR5 and CXCR4, leading to an increase in ROS and TGFβ1 signaling. This stimulates HSCs to activate and produce ECM through upregulation of genes CoL1A1 and TIMP1. HIV-induced apoptosis of hepatocytes and subsequent phagocytosis by macrophages and HSCs also promote HSC transdifferentiation to its activated form. HIV can directly infect HSCs through CCR5 dependent and independent pathways, as well as Kupffer cells through TLR4, to stimulate ECM production and fibrogenesis. The latter process is represented by elevation of sCD163 levels. b. Microbial translocation. Bacterial translocation is induced by HIV through CD4 depletion in the intestinal tract, tight junction disruption, and enterocyte apoptosis. LPS endotoxins in the portal circulation are drained by the liver and activate Kupffer cells and HSCs through TLR4 interactions. c. Altered immunity. HIV-HCV co-infected patients have decreased NK cell frequency and impaired functional activity, which prevents killing of HSCs and promotes their survival. Additionally, chronic HIV leads to high levels of CD4 and CD8 activation, then exhaustion as represented by CD39 and PD1, then death. These contribute to HCV persistence and further fibrogenesis. CCR5, CC-motif chemokine receptor 5; CXCR4, C-X-C motif chemokine receptor 4; ROS, reactive oxygen species; TGFβ1, transforming growth factor beta-1; ECM, extracellular matrix; CoL1A1, collagen type 1 α 1; TIMP1, TIMP metallopeptidase inhibitor 1; HSC, hepatic stellate cell; TLR4, toll-like receptor 4; sCD163, soluble CD163; LPS, lipopolysaccharide; HCV, hepatitis C virus; NK cell, natural killer cell.

antigens and increased rates of HCV persistence [21]. In addition, chronic HIV infection is characterized by high levels of CD4 and CD8 T cell activation, eventually leading to T cell exhaustion, depletion, and death [22]. CD39 and PD-1, markers of T-cell exhaustion, are abundantly expressed by CD8 T-cells in HIV and HCV and correlate with high levels of viral load [23], and co-infected patients have significantly higher rates of CD4 and CD8 T-cell apoptosis compared to HIV-mono-infected patients [24]. Similarly, PD-L1 levels were significantly higher in HIV-HBV co-infection compared to healthy controls [25]. HIV-HCV co-infected patients also have decreased natural killer cell frequency and highly impaired natural killer cell functional activity, which promotes activated HSC survival and liver fibrosis progression [26–28].

Viral hepatitis (hepatitis C virus, hepatitis B virus, hepatitis delta virus, and hepatitis E virus)

Viral hepatitides remain significant contributors to liver disease in PLWH, with an increased prevalence of all forms in this population. We will focus on

those that cause chronic infection: HCV, HBV, HDV, and HEV while noting that acute injury from these and other viruses (e.g., hepatitis A) also can lead to long-lasting hepatic fibrosis in some cases.

As reviewed above, HIV synergistically accelerates fibrosis progression in HCV co-infection, leading to both decompensated cirrhosis and hepatocellular carcinoma (HCC). In addition, HCV co-infection increases the risk of all-cause and liver-related mortality in PLWH [29]. The prevalence of HIV-HCV co-infection among HIV-infected individuals was previously estimated to be 20% in North America and more than 80% among those with injection drug use [30]. Recent estimates are lacking; effective treatment reduces chronic infection rates, but new infections associated with injection drug use and high risk sexual behaviors among men who have sex with men contribute to a new pool of chronic HCV. In the era of DAA regimens, HCV treatment is tolerable and highly efficacious, with SVR rates in co-infected individuals similar to HCV mono-infected patients and upwards of 90%. Though the applicability of results from clinical trials to the real world has been questioned, a systematic review showed similar SVR between real-world and clinical trial studies in HIV-HCV co-infection [31]. Effective HCV treatment in co-infected patients has been associated with improved measures of fibrosis and mortality [32,33], and in prospective studies, the risk of liver complications and HCC after SVR in HIV-HCV co-infected patients with cirrhosis is no longer higher than the risk for HCV mono-infected patients [34,35]. Despite the clinical benefits, however, elevation in inflammatory and fibrotic biomarkers persist after HCV clearance, which suggests the need for continued monitoring for fibrosis progression in the co-infected population [36].

In North America, the prevalence of HBV co-infection in PLWH ranges from 4–10%, but the greatest burden lies in sub-Saharan Africa with a prevalence of 69% [37]. HBV infection is a significant contributor to end-stage liver disease in patients with HIV, as well as increased liver-related death [38,39]. Tenofovir is often a key element in the backbone of antiretroviral therapy (ART) regimens and is effective for long-term treatment of HBV, particularly given high rates of resistance to lamivudine and emtricitabine due to YMDD mutations [40,41]. In a recent prospective study of HIV-HBV co-infected patients on cART with anti-HBV activity and long-term viral suppression, clinical events and histologic changes were uncommon [42▪]. Despite this, the North American AIDS Cohort Collaboration study found no clear reduction in end-stage liver disease risk, and notably over one-third of HBV-coinfected patients were not receiving tenofovir [38]. Additionally, there has been recent interest in simplifying ART to 2-drug regimens, such as dolutegravir-rilpivirine or dolutegravir-lamivudine [43]. These studies note the importance of excluding patients with chronic HBV infection, as inadvertently transitioning patients with previously suppressed HBV infection to a regimen without effective activity against HBV can result in severe hepatitis flares [44]. However, these cART switches are anecdotally occurring with some frequency due to a lack of recognition that HBV had been previously present but suppressed. Suboptimal HBV vaccination use and poor HBV vaccine efficacy in PLWH remain a challenge, with ongoing studies to improve seroprotection rates [45,46].

HDV infection only occurs as a superinfection or coinfection with HBV. Global estimated prevalence is 5% among people with chronic HBV [47], and in Europe around 15% of patients with HIV and chronic HBV infection were anti-HDV positive [48]. Studies have shown increased risk of hepatic decompensation, HCC, and liver-related death in HIV/HBV/HDV triple infection compared to people without HDV, even in analyses limited to patients on optimal HBV therapy [48–50]. The Swiss HIV cohort study found that over a 9-year follow-up period of patients on ART, those with HDV infection were twice as likely to die as those without HDV [49], which outlines the importance of prevention and effective treatment. Bulevirtide and lonafarnib have emerged as new treatment options that have been recently approved or are undergoing review by regulatory agencies in the USA and Europe.

HEV has become the most common cause of acute viral hepatitis in many European countries and is mostly attributable to exposure to undercooked swine products, though consumption of rabbits and other infected species may also be a factor in some locations [51]. HEV infection is usually self-limited, but chronic infection with HEV genotype 3 has been seen in immunosuppressed patients such as those with HIV or solid organ transplantation [52–54]. Prevalence of chronic HEV infection in PLWH according to studies in Europe and the United States have ranged from 0.1 to 0.5%, with CD4 count less than 200 identified as a risk factor [55]. Two cases of HIV-HEV co-infection have been described with cirrhosis development in less than 3 years in the setting of severe immunosuppression [56], and HEV should be considered in cases of cryptogenic cirrhosis in HIV-infected patients. Test modalities are suboptimal, however, and HEV RNA should be obtained whenever chronic HEV is part of the differential diagnosis for injury and fibrosis.

Fatty liver (alcohol and nonalcoholic fatty liver disease)

With effective HCV cure and rising rates of obesity, fatty liver disease has become an increasingly recognized contributor to liver disease in persons with HIV. Broadly, fatty liver disease can be differentiated into alcohol and nonalcoholic steatosis. NAFLD represents a spectrum of disease, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. NAFLD is more prevalent in HIV-infected patients than the general population, affecting over one-third of HIV mono-infected patients [57]. In addition, half of those with chronic aminotransferase elevations had NASH on biopsies [58]. PLWH have similar risk factors for NAFLD as the general population, such as higher body mass index (BMI), insulin resistance, and PNPLA3 polymorphisms [57–59]. Importantly, some studies have shown that NAFLD in HIV-infected patients occurs at a significantly lower BMI than those without HIV [60].

Notably, Fourman and colleagues recently found that HIV-associated NAFLD was not only associated with a high prevalence of fibrosis but also rapid fibrosis progression [61▪▪]. On initial biopsies, 43% had evidence of hepatic fibrosis, and within 1 year 38% experienced worsening of hepatic fibrosis on repeat biopsies regardless of baseline presence of fibrosis. The rate of fibrosis progression in HIV-associated NAFLD was accelerated compared to the rate found in a systematic review for NASH in the general population [61▪▪]. In this study, visceral fat was found to be a significant predictor of fibrosis presence and progression.

Lipodystrophy, characterized by central accumulation and/or peripheral loss of adipose tissue, is common in patients with HIV. HIV-associated lipodystrophy is associated with insulin resistance and dyslipidemia and can occur due to ART, direct HIV effects, and microbial translocation (Fig. 2) [62]. Visceral fat is proinflammatory and profibrotic [61▪▪], and lipolysis of peripheral adipose tissue can increase the hepatic influx of free fatty acids, leading to steatohepatitis [36]. In addition to the fibrogenic pathways previously described, LPS from HIV-associated microbial translocation may also contribute to NAFLD development through increases in insulin resistance, liver triglyceride content, and adipose tissue inflammation [63].

While the criteria for NAFLD excludes heavy alcohol use, alcohol is also an important factor in hepatic steatosis. Alcohol use is prevalent among PLWH, including higher amounts of heavy use compared to the general population [64], and is associated with decreased adherence to ART and viral suppression [65]. Heavy alcohol use clearly leads to faster rates of fibrosis progression [66]. Like HIV-associated microbial translocation, ethanol metabolism can induce intestinal barrier dysfunction, endotoxemia, and HSC and macrophage activation with synergistic liver damage by ethanol and LPS [67]. Additionally, ethanol metabolism has been shown to potentiate apoptosis of HIV-containing hepatocytes *in-vitro*, which contributes to progression of inflammation and fibrosis [68].

ROLE OF HIV SUPPRESSION AND ANTIRETROVIRAL THERAPY ON FIBROSIS

The use of cART and effective viral suppression have generally been shown to lower the risk of hepatic fibrosis progression. HIV viral suppression was associated with a significant decline in hepatic inflammation prior to an increase in CD4 counts among HIV-HCV co-infected patients treated with cART [69]. Two large cohort studies, including the START study with over 4500 participants and a study by Ding *et al.* with 3900 participants, showed that early cART initiation was correlated with decreased fibrosis progression by Fibrosis-4 (FIB-4) and AST to platelet ratio index scores [70,71]. Likewise, ART interruption resulted in an increased risk of fibrosis progression [72].

However, studies have also shown that mechanisms of fibrogenesis persist despite ART. Continued elevation of serum immune activation markers and incomplete recovery of CD4 T-cells in intestinal mucosa are seen despite long-term effective viral suppression with ART [73,74]. Soluble CD163 levels, which are significantly associated with hepatic fibrosis [14], are incompletely reduced after ART and HCV therapy in HIV-HCV co-infected patients, implicating residual Kupffer cell activation despite HIV viral suppression [13]. HIV suppression with cART does significantly decrease the rate of hepatic decompensation, but rates are still higher in HIV-HCV co-infected patients than in HCV mono-infected patients [75,76].

ART can also cause drug-related liver injury. In addition to mitochondrial toxicity from first-generation nucleoside reverse transcriptase inhibitors (NRTIs) [77], older ART therapy, such as NRTIs and protease inhibitors, can induce irreversible insulin resistance and lipodystrophy, leading to hepatic steatosis and NAFLD development, fibrosis, and hepatic decompensation [78–81]. This is particularly relevant to long-term HIV survivors and those in resource-constrained settings where these agents are still used. Non-NRTI efavirenz can similarly cause mitochondrial injury, hepatic lipid accumulation, and steatosis progression [82,83]. Integrase strand transfer inhibitors (INSTIs), which are now

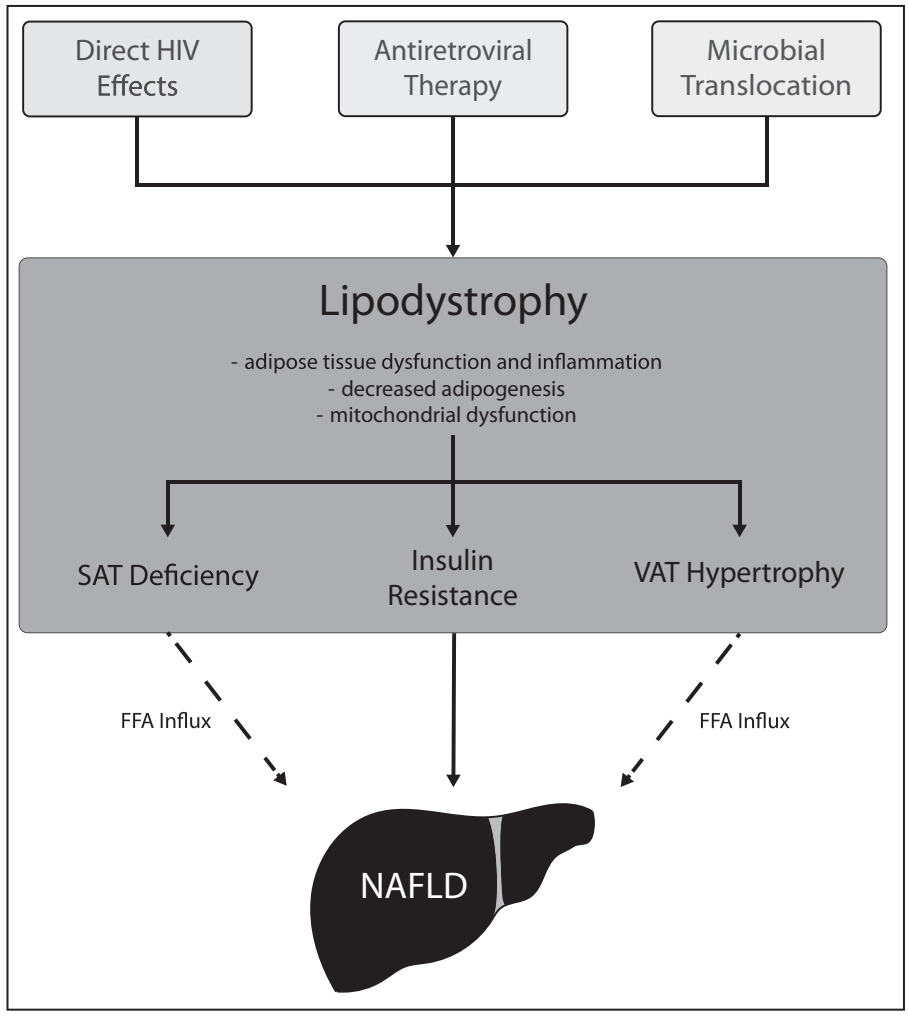

FIGURE 2. Direct HIV effects, antiretroviral therapy, and microbial translocation all contribute to the pathogenesis of HIV lipodystrophy through adipose tissue dysfunction and inflammation, decrease in adipogenesis, and mitochondrial dysfunction. These manifest as SAT deficiency and VAT hypertrophy, which lead to lipid overflow and hepatic influx of FFAs, as well as insulin resistance. These factors play important roles in the development of HIV-associated NAFLD. SAT, subcutaneous adipose tissue; VAT, visercal adipose tissue; FFA, free fatty acid; NAFLD, nonalcoholic fatty liver disease.

first-line in most ART regimens, can be associated with weight gain after ART initiation or switch to INSTI, with dolutegravir as the main implicated agent [84–86]. Data so far on the subsequent impact on liver steatosis and NAFLD are mixed [87,88].

THERAPEUTIC INTERVENTIONS FOR HEPATIC FIBROSIS

Inclusion of an agent with CCR5 blockade in an antiretroviral regimen may provide an additional antifibrotic effect. HIV binds to CCR5 receptors on hepatocytes and stellate cells, triggering proinflammatory and profibrotic pathways. Maraviroc, a CCR5 inhibitor, has been shown to block collagen and ECM accumulation in stellate cells [89] and improve or blunt development of hepatic fibrosis markers in HIV-HCV co-infection [90,91]. Similarly in a phase 2 trial, patients with HIV treated with cenicriviroc (CVC), a CCR5 and CCR2 dual antagonist, showed a significant improvement in hepatic fibrosis biomarkers compared to use of an efavirenz-based regimen [92,93]. In non-HIV infected patients with NASH, CVC improved fibrosis without an effect on steatohepatitis [94]. Pending results of phase 3 trials, this suggests that CVC may be considered in the ART regimen for patients with HIV and NASH.

Tesamorelin, a growth hormone releasing analog administered subcutaneously once daily and approved by the United States Food and Drug Administration (FDA) for HIV lipodystrophy, is an emerging therapy for HIV-associated NAFLD. Due to perturbations in growth hormone secretion with reduced pulsatile growth hormone in PLWH, weight

gain and abdominal fat accumulation occur. Tesamorelin restores endogenous pulsatile growth hormone secretion and reduces visceral adiposity by stimulating lipolysis in HIV-infected patients [95]. Correspondingly, it has been shown to reduce liver fat content and prevent fibrosis progression [96]. Long-term treatment with tesamorelin also notably decreased markers of T-cell and monocyte/macrophage activity, suggesting reduction in immune activation and systemic inflammation in patients with HIV and NAFLD [97▪▪]. Other classes of agents for NAFLD/NASH or reduction of hepatic fibrosis are under active evaluation (e.g., FXR agonists, thyroid hormone receptor agonists) in non-HIV infected populations and also show promising results, but studies in PLWH are lacking.

The potential for hepatitis D cure has generated excitement in the field, especially considering the rapid progression of liver disease from HDV and prior lack of effective therapy. Bulevirtide, a once daily subcutaneous drug that blocks entry of HBV/HDV into hepatocytes, was recently approved in Europe for HDV treatment with some cases demonstrating potential for cure [98]. Lonafarnib, an oral farnesyl transferase inhibitor that blocks HDV assembly in hepatocytes, is undergoing a global phase 3 clinical trial for treatment of HDV [99]. A one-time ultra-long acting formulation has been proposed by Soriano and colleagues as an attainable future prospect for HDV cure [100].

CONCLUSION

Liver disease continues to be a major source of morbidity and mortality among PLWH. Key contributors to injury and development of fibrosis have evolved over the last two decades. While some disease processes like HCV are receding in significance due to the presence of effective curative treatments, other diseases have emerged in importance. Hepatic fibrosis is the endpoint in injury from a host of interrelated etiologies, leading to development of cirrhosis and subsequently end-stage liver disease. Future clinical and research needs include improved recognition of chronic viral infections, cure strategies for hepatitis B and D, better understanding of processes that cause simple steatosis to develop into inflammatory NAFLD/NASH in people with HIV, and HIV treatment regimens that protect the liver rather than cause harm. Promising antifibrotic agents are on the horizon, but focus on PLWH has been relatively limited. Pending HIV cure strategies, investment in the reduction of liver disease and prevention of fibrosis development remain key targets for the health and safety of persons living with HIV.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

1. Smith CJ, Ryom L, Weber R, *et al.* Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. Lancet 2014; 384:241–248.
2. Kisseleva T, Brenner D. Molecular and cellular mechanisms of liver fibrosis and its regression. Nat Rev Gastroenterol Hepatol 2021; 18:151–166.
3. Krizhanovsky V, Yon M, Dickins RA, *et al.* Senescence of activated stellate cells limits liver fibrosis. Cell 2008; 134:657–667.
4. Kong L, Cardona Maya W, Moreno-Fernandez ME, *et al.* Low-level HIV infection of hepatocytes. Virol J 2012; 9:157.
5. Lin W, Wu G, Li S, *et al.* HIV and HCV cooperatively promote hepatic fibrogenesis via induction of reactive oxygen species and NFκB. J Biol Chem 2011; 286:2665–2674.
6. Salloum S, Holmes JA, Jindal R, *et al.* Exposure to human immunodeficiency virus/hepatitis C virus in hepatic and stellate cell lines reveals cooperative profibrotic transcriptional activation between viruses and cell types. Hepatology 2016; 64:1951–1968.
7. Vlahakis SR, Villasis-Keever A, Gomez TS, *et al.* Human immunodeficiency virus–induced apoptosis of human hepatocytes via CXCR4. J Infect Dis 2003; 188:1455–1460.
8. Zhan S, Jiang JX, Wu J, *et al.* Phagocytosis of apoptotic bodies by hepatic stellate cells induces NADPH oxidase and is associated with liver fibrosis in vivo. Hepatology 2006; 43:435–443.
9. Bruno R, Galastri S, Sacchi P, *et al.* gp120 modulates the biology of human hepatic stellate cells: a link between HIV infection and liver fibrogenesis. Gut 2010; 59:513–520.
10. Tuyama AC, Hong F, Saiman Y, *et al.* Human immunodeficiency virus (HIV)-1 infects human hepatic stellate cells and promotes collagen I and monocyte chemoattractant protein-1 expression: Implications for the pathogenesis of HIV/hepatitis C virus–induced liver fibrosis. Hepatology 2010; 52:612–622.
11. Del Cornò M, Cappon A, Donninelli G, *et al.* HIV-1 gp120 signaling through TLR4 modulates innate immune activation in human macrophages and the biology of hepatic stellate cells. J Leukoc Biol 2016; 100:599–606.
12. Mosoian A, Zhang L, Hong F, *et al.* Frontline science: HIV infection of Kupffer cells results in an amplified proinflammatory response to LPS. J Leukoc Biol 2017; 101:1083–1090.
13. Lidofsky A, Holmes JA, Feeney ER, *et al.* Macrophage activation marker soluble CD163 is a dynamic marker of liver fibrogenesis in human immunodeficiency virus/hepatitis C virus coinfection. J Infect Dis 2018; 218:1394–1403.
14. Sherman KE, Meeds HL, Rouster SD, *et al.* Soluble CD163 identifies those at risk for increased hepatic inflammation & fibrosis. Open Forum Infect Dis 2021; 8.:ofab203.
15. Balagopal A, Philp FH, Astemborski J, *et al.* Human immunodeficiency virus-related microbial translocation and progression of hepatitis C. Gastroenterology 2008; 135:226–233.
16. Brenchley JM, Paiardini M, Knox KS, *et al.* Differential Th17 CD4 T-cell depletion in pathogenic and nonpathogenic lentiviral infections. Blood 2008; 112:2826–2835.
17. Vujkovic-Cvijin I, Dunham RM, Iwai S, *et al.* Dysbiosis of the gut microbiota is associated with HIV disease progression and tryptophan catabolism. Sci Transl Med 2013; 5:193ra91.

18. Marchetti G, Tincati C, Silvestri G. Microbial translocation in the pathogenesis of HIV infection and AIDS. Clin Microbiol Rev 2013; 26:2–18.
19. Douek DC, Brenchley JM, Price DA, *et al.* Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med 2006; 12:1365–1371.
20. Seki E, De Minicis S, Oesterreicher C, *et al.* TLR4 enhances TGF-b signaling and hepatic fibrosis. Nat Med 2007; 13:1324–1332.
21. Danta M, Semmo N, Fabris P, *et al.* Impact of HIV on host-virus interactions during early hepatitis C virus infection. J Infect Dis 2008; 197:1558–1566.
22. Douek DC, Picker LJ, Koup RA. T cell dynamics in HIV-1 infection. Annu Rev Immunol 2003; 21:265–304.
23. Gupta PK, Godec J, Wolski D, *et al.* CD39 expression identifies terminally exhausted CD8+ T cells. PLOS Pathog 2015; 11:e1005177.
24. Núñez M, Soriano V, López M, *et al.* Coinfection with hepatitis C virus increases lymphocyte apoptosis in HIV-infected patients. Clin Infect Dis 2006; 43:1209–1212.
25. Shata MTM, Abdel-Hameed EA, Rouster SD, *et al.* HBV and HIV/HBV infected patients have distinct immune exhaustion and apoptotic serum biomarker profiles. Pathog Immun 2019; 4:39–65.
26. Kaczmarek DJ, Kokordelis P, Krämer B, *et al.* Alterations of the NK cell pool in HIV/HCV co-infection. PLoS One 2017; 12:e0174465.
27. Glässner A, Eisenhardt M, Kokordelis P, *et al.* Impaired $CD4^+$ T cell stimulation of NK cell antifibrotic activity may contribute to accelerated liver fibrosis progression in HIV/HCV patients. J Hepatol 2013; 59:427–433.
28. Polo ML, Ghiglione YA, Salido JP, *et al.* Liver cirrhosis in HIV/HCV-coinfected individuals is related to NK cell dysfunction and exhaustion, but not to an impaired NK cell modulation by CD4+ T-cells. J Int AIDS Soc 2019; 22:e25375.
29. Hernando V, Perez-Cachafeiro S, Lewden C, *et al.* All-cause and liver-related mortality in HIV positive subjects compared to the general population: differences by HCV co-infection. J Hepatol 2012; 57:743–751.
30. Platt L, Easterbrook P, Gower E, *et al.* Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. Lancet Infect Dis 2016; 16:797–808.
31. Sikavi C, Najarian L, Saab S. Similar sustained virologic response in real-world and clinical trial studies of hepatitis c/human immunodeficiency virus coinfection. Dig Dis Sci 2018; 63:2829–2839.
32. Kovari H, Ledergerber B, Cavassini M, *et al.* High hepatic and extrahepatic mortality and low treatment uptake in HCV-coinfected persons in the Swiss HIV cohort study between 2001 and 2013. J Hepatol 2015; 63:573–580.
33. Rial-Crestelo D, Sepúlveda MA, González-Gasca FJ, *et al.* Does fibrosis really regress in HIV/hepatitis C virus co-infected patients after treatment with direct antiviral agents? AIDS 2020; 34:427–432.
34. Corma-Gómez A, Morano L, Téllez F, *et al.* HIV infection does not increase the risk of liver complications in hepatitis C virus-infected patient with advanced fibrosis, after sustained virological response with direct-acting antivirals. AIDS (London) 2019; 33:1167–1174.
35. Salmon-Ceron D, Nahon P, Layese R, *et al.* Human immunodeficiency virus/hepatitis C virus (HCV) co-infected patients with cirrhosis are no longer at higher risk for hepatocellular carcinoma or end-stage liver disease as compared to hcv mono-infected patients. Hepatology 2019; 70:939–954.
36. Jeyarajan AJ, Chung RT. Insights into the pathophysiology of liver disease in HCV/HIV: does it end with HCV cure? J Infect Dis 2020; 222:S802–S813.
37. Platt L, French CE, McGowan CR, *et al.* Prevalence and burden of HBV co-infection among people living with HIV: a global systematic review and meta-analysis. J Viral Hepat 2020; 27:294–315.
38. Klein MB, Althoff KN, Jing Y, *et al.* Risk of end-stage liver disease in HIV-viral hepatitis coinfected persons in North America from the early to modern antiretroviral therapy eras. Clin Infect Dis 2016; 63:1160–1167.
39. Thio CL, Seaberg EC, Skolasky R, *et al.* HIV-1, hepatitis B virus, and risk of liver-related mortality in the multicenter cohort study (MACS). Lancet 2002; 360:1921–1926.
40. Saravolatz LD, Saag MS. Emtricitabine, a new antiretroviral agent with activity against HIV and hepatitis B virus. Clin Infect Dis 2006; 42:126–131.
41. Benhamou Y, Bochet M, Thibault V, *et al.* Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. Hepatology 1999; 30:1302–1306.
42. ■ Sterling RK, King WC, Khalili M, *et al.* A Prospective study evaluating changes in histology, clinical and virologic outcomes in HBV-HIV co-infected adults in North America. Hepatology 2021; 74:1174–1189.

This prospective multicenter study is one of few studies that evaluated clinical outcomes and fibrosis progression in HIV-HBV co-infection on stable cART with paired liver biopsies despite the challenges of studying this population.

43. Corado KC, Caplan MR, Daar ES. Two-drug regimens for treatment of naïve HIV-1 infection and as maintenance therapy. Drug Des Devel Ther 2018; 12:3731–3740.
44. Bessesen M, Ives D, Condreay L, *et al.* Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine. Clin Infect Dis 1999; 28:1032–1035.
45. Launay O, Rosenberg AR, Rey D, *et al.* Long-term immune response to hepatitis B virus vaccination regimens in adults with human immunodeficiency virus 1: secondary analysis of a randomized clinical trial. JAMA Intern Med 2016; 176:603–610.
46. Schnittman SR, Zepf R, Cocohoba J, Sears D. Brief report: heplisav-b seroprotection in people with HIV: a single-center experience. J Acquir Immune Defic Syndr 2021; 86:445–449.
47. Stockdale AJ, Kreuels B, Henrion MYR, *et al.* The global prevalence of hepatitis D virus infection: systematic review and meta-analysis. J Hepatol 2020; 73:523–532.
48. Soriano V, Grint D, d'Arminio Monforte A, *et al.* Hepatitis delta in HIV-infected individuals in Europe. AIDS 2011; 25:1987–1992.
49. Béguelin C, Moradpour D, Sahli R, *et al.* Hepatitis delta-associated mortality in HIV/HBV-coinfected patients. J Hepatol 2016; 66:297–303.
50. Fernández-Montero JV, Vispo E, Barreiro P, *et al.* Hepatitis delta is a major determinant of liver decompensation events and death in HIV-infected patients. Clin Infect Dis 2014; 58:1549–1553.
51. Dalton HR, Kamar N, Baylis SA, *et al.* EASL clinical practice guidelines on hepatitis E virus infection. J Hepatol 2018; 68:1256–1271.
52. Kenfak-Foguena A, Schöni-Affolter F, Bürgisser P, *et al.* Hepatitis E virus seroprevalence and chronic infections in patients with HIV, Switzerland. Emerg Infect Dis 2011; 17:1074–1078.
53. Jagjit Singh GK, Ijaz S, Rockwood N, *et al.* Chronic Hepatitis E as a cause for cryptogenic cirrhosis in HIV. J Infect 2013; 66:103–106.
54. Kamar N, Garrouste C, Haagsma EB, *et al.* Factors associated with chronic hepatitis in patients with hepatitis E virus infection who have received solid organ transplants. Gastroenterology 2011; 140:1481–1489.
55. Rivero-Juarez A, Lopez-Lopez P, Frias M, Rivero A. Hepatitis E infection in HIV-infected patients. Front Microbiol 2019; XX:10.
56. Neukam K, Barreiro P, Macías J, *et al.* Chronic hepatitis E in HIV patients: rapid progression to cirrhosis and response to oral ribavirin. Clin Infect Dis 2013; 57:465–468.
57. Maurice JB, Patel A, Scott AJ, *et al.* Prevalence and risk factors of nonalcoholic fatty liver disease in HIV-monoinfection. AIDS 2017; 31:1621–1632.
58. Morse CG, McLaughlin M, Matthews L, *et al.* Nonalcoholic steatohepatitis and hepatic fibrosis in HIV-1–monoinfected adults with elevated aminotransferase levels on antiretroviral therapy. Clin Infect Dis 2015; 60:1569–1578.
59. Price JC, Seaberg EC, Latanich R, *et al.* Risk factors for fatty liver in the multicenter AIDS cohort study. Am J Gastroenterol 2014; 109:695–704.
60. Mohammed SS, Aghdassi E, Salit IE, *et al.* HIV-positive patients with nonalcoholic fatty liver disease have a lower body mass index and are more physically active than HIV-negative patients. J Acquir Immune Defic Syndr 2007; 45:432–438.
61. ■■ Fourman LT, Stanley TL, Zheng I, *et al.* Clinical predictors of liver fibrosis presence and progression in human immunodeficiency virus–associated nonalcoholic fatty liver disease. Clin Infect Dis 2020; 72:2087–2094.

This study is the first longitudinal assessment of HIV-associated NAFLD and the first to utilize serial liver biopsies to determine the natural history of this population. This article demonstrated high prevalence of fibrosis and rapid progression of fibrosis in this group.

62. Lake JE, Overton T, Naggie S, *et al.* Expert panel review on nonalcoholic fatty liver disease in persons with human immunodeficiency virus. Clin Gastroenterol Hepatol 2022; 20:256–268.
63. Cani PD, Amar J, Iglesias MA, *et al.* Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 2007; 56:1761–1772.
64. Chander G, Josephs J, Fleishman JA, *et al.* Alcohol use among HIV-infected persons in care: results of a multisite survey*. HIV Med 2008; 9:196–202.
65. Chander G, Lau B, Moore R. Hazardous alcohol use: a risk factor for non-adherence and lack of suppression in HIV infection. J Acquir Immune Defic Syndr 19992006; 43:411–417.
66. Kelly EM, Dodge JL, Bacchetti P, *et al.* Moderate alcohol use is not associated with fibrosis progression in human immunodeficiency virus/hepatitis C virus-coinfected women: a prospective cohort study. Clin Infect Dis 2017; 65:2050–2056.
67. Rao R. Endotoxemia and gut barrier dysfunction in alcoholic liver disease. Hepatology 2009; 50:638–644.
68. Ganesan M, New-Aaron M, Dagur RS, *et al.* Alcohol metabolism potentiates HIV-induced hepatotoxicity: contribution to end-stage liver disease. Biomolecules 2019; 9:851.
69. Sherman KE, Guedj J, Shata MT, *et al.* Modulation of HCV replication after combination antiretroviral therapy in HCV/HIV coinfected patients. Sci Transl Med 2014; 6:246ra98.
70. Dharan NJ, Neuhaus J, Rockstroh JK, *et al.* Benefit of early versus deferred antiretroviral therapy on progression of liver fibrosis among people with HIV in the START randomized trial. Hepatology 2019; 69:1135–1150.
71. Ding Y, Duan S, Ye R, *et al.* More improvement than progression of liver fibrosis following antiretroviral therapy in a longitudinal cohort of HIV-infected patients with or without HBV and HCV co-infections. J Viral Hepat 2017; 24:412–420.
72. Thorpe J, Saeed S, Moodie EEM, Klein MB. Antiretroviral treatment interruption leads to progression of liver fibrosis in HIV-hepatitis C virus co-infection. AIDS 2011; 25:967–975.
73. French MA, King MS, Tschampa JM, *et al.* Serum immune activation markers are persistently increased in patients with HIV infection after 6 years of antiretroviral therapy despite suppression of viral replication and reconstitution of CD4+ T cells. J Infect Dis 2009; 200:1212–1215.

74. Chun T, Nickle DC, Justement JS, *et al.* Persistence of HIV in gut-associated lymphoid tissue despite long-term antiretroviral therapy. J Infect Dis 2008; 197:714–720.

75. Lo Re V, Kallan MJ, Tate JP, *et al.* Hepatic decompensation in antiretroviral-treated patients co-infected with HIV and hepatitis C virus compared with hepatitis C virus-monoinfected patients: a cohort study. Ann Intern Med 2014; 160:369–379.

76. Anderson JP, Tchetgen Tchetgen EJ, Lo Re V, *et al.* Antiretroviral therapy reduces the rate of hepatic decompensation among HIV- and hepatitis C virus–coinfected veterans. Clin Infect Dis 2014; 58:719–727.

77. Lewis W, Day BJ, Copeland WC. Mitochondrial toxicity of NRTI antiviral drugs: an integrated cellular perspective. Nat Rev Drug Discov 2003; 2:812–822.

78. Margolis AM, Heverling H, Pham PA, Stolbach A. A review of the toxicity of HIV medications. J Med Toxicol 2014; 10:26–39.

79. Guaraldi G, Squillace N, Stentarelli C, *et al.* Nonalcoholic fatty liver disease in HIV-infected patients referred to a metabolic clinic: prevalence, characteristics, and predictors. Clin Infect Dis 2008; 47:250–257.

80. Carr A, Samaras K, Burton S, *et al.* A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 1998; 12:F51–F58.

81. Re VL, Zeldow B, Kallan MJ, *et al.* Risk of liver decompensation with cumulative use of mitochondrial toxic nucleoside analogues in HIV/hepatitis C virus coinfection. Pharmacoepidemiol Drug Saf 2017; 26:1172–1181.

82. Blas-García A, Apostolova N, Ballesteros D, *et al.* Inhibition of mitochondrial function by efavirenz increases lipid content in hepatic cells. Hepatology 2010; 52:115–125.

83. Macías J, Berenguer J, Japón MA, *et al.* Hepatic steatosis and steatohepatitis in human immunodeficiency virus/hepatitis C virus–coinfected patients. Hepatology 2012; 56:1261–1270.

84. Bourgi K, Jenkins CA, Rebeiro PF, *et al.* Weight gain among treatment-naïve persons with HIV starting integrase inhibitors compared to nonnucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada. J Int AIDS Soc 2020; 23:e25484.

85. Norwood J, Turner M, Bofill C, *et al.* Weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. J Acquir Immune Defic Syndr 2017; 76:527–531.

86. Menard A, Meddeb L, Tissot-Dupont H, *et al.* Dolutegravir and weight gain: an unexpected bothering side effect? AIDS 2017; 31:1499–1500.

87. Kirkegaard-Klitbo DM, Thomsen MT, Gelpi M, *et al.* Hepatic steatosis associated with exposure to elvitegravir and raltegravir. Clin Infect Dis 2021; 73:e811–e814.

88. Macías J, Mancebo M, Merino D, *et al.* Changes in liver steatosis after switching from efavirenz to raltegravir among human immunodeficiency virus-infected patients with nonalcoholic fatty liver disease. Clin Infect Dis 2017; 65:1012–1019.

89. Coppola N, Perna A, Lucariello A, *et al.* Effects of treatment with maraviroc a CCR5 inhibitor on a human hepatic stellate cell line. J Cell Physiol 2018; 233:6224–6231.

90. Ortega Gonzalez E, Boix V, Garcia Deltoro M, *et al.* The effects of maraviroc on liver fibrosis in HIV/HCV co-infected patients. J Int AIDS Soc 2014; 17:19643.

91. Macías J, Viloria MM, Rivero A, *et al.* Lack of short-term increase in serum mediators of fibrogenesis and in noninvasive markers of liver fibrosis in HIV/hepatitis C virus-coinfected patients starting maraviroc-based antiretroviral therapy. Eur J Clin Microbiol Infect Dis 2012; 31:2083–2088.

92. Thompson M, Saag M, DeJesus E, *et al.* A 48-week randomized phase 2b study evaluating cenicriviroc versus efavirenz in treatment-naive HIV-infected adults with C-C chemokine receptor type 5-tropic virus. AIDS 2016; 30:869–878.

93. Sherman KE, Abdel-Hameed E, Rouster SD, *et al.* Improvement in hepatic fibrosis biomarkers associated with chemokine receptor inactivation through mutation or therapeutic blockade. Clin Infect Dis 2019; 68: 1911–1918.

94. Friedman SL, Ratziu V, Harrison SA, *et al.* A randomized, placebo-controlled trial of cenicriviroc for treatment of nonalcoholic steatohepatitis with fibrosis. Hepatology 2018; 67:1754–1767.

95. Falutz J, Mamputu J, Potvin D, *et al.* Effects of tesamorelin (TH9507), a growth hormone-releasing factor analog, in human immunodeficiency virus-infected patients with excess abdominal fat: a pooled analysis of two multicenter, double-blind placebo-controlled phase 3 trials with safety extension data. J Clin Endocrinol Metab 2010; 95:4291–4304.

96. Stanley TL, Fourman LT, Feldpausch MN, *et al.* Effects of tesamorelin on nonalcoholic fatty liver disease in HIV: a randomised, double-blind, multicentre trial. Lancet HIV 2019; 6:e821–e830.

97. ■■ Stanley TL, Fourman LT, Wong LP, *et al.* Growth hormone releasing hormone reduces circulating markers of immune activation in parallel with effects on hepatic immune pathways in individuals with HIV-infection and nonalcoholic fatty liver disease. Clin Infect Dis 2021; 73:621–630.

This study demonstrated that beyond improvement in liver fat and fibrosis in HIV-associated NAFLD with tesamorelin, the agent decreases markers of T-cell monocyte/macrophage activity, which suggests strong systemic anti-inflammatory effects.

98. Wedemeyer H, Schöneweis K, Bogomolov PO, *et al.* 48 weeks of high dose (10 mg) bulevirtide as monotherapy or with peginterferon alfa-2a in patients with chronic HBV/HDV co-infection. J Hepatol 2020; 73:S52–S53.

99. Yurdaydin C, Keskin O, Kalkan Ç, *et al.* Optimizing lonafarnib treatment for the management of chronic delta hepatitis: the LOWR HDV-1 study. Hepatology 2018; 67:1224–1236.

100. Soriano V, de Mendoza C, Treviño A, *et al.* Treatment of hepatitis delta and HIV infection. Liver Int 2022; XX:XX.