Review Article

Mechanisms of Accelerated Liver Fibrosis Progression during HIV Infection

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Abstract

With the introduction of antiretroviral therapy (ART), a dramatic reduction in HIV-related morbidity and mortality has been observed. However, it is now becoming increasingly clear that liver-related complications, particularly rapid fibrosis development from ART as well as from the chronic HIV infection itself, are of serious concern to HIV patients. The pathophysiology of liver fibrosis in patients with HIV is a multifactorial process whereby persistent viral replication, and bacterial translocation lead to chronic immune activation and inflammation, which ART is unable to fully suppress, promoting production of fibrinogenic mediators and fibrosis. In addition, mitochondrial toxicity, triggered by both ART and HIV, contributes to intrahepatic damage, which is even more severe in patients co-infected with viral hepatitis. In recent years, new insights into the mechanisms of accelerated fibrosis and liver disease progression in HIV has been obtained, and these are detailed and discussed in this review. © 2016 The Second Affiliated Hospital of Chongqing Medical University. Published by XIA & HE Publishing Inc. All rights reserved.

Introduction

Liver disease is a major cause of morbidity and the main cause of mortality, independent of acquired immunodeficiency syndrome (AIDS), in persons infected with the human immunodeficiency virus (HIV), with liver fibrosis being a highly significant contributor.[1] Although HIV co-infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is frequent, there is mounting evidence of an increased risk in liver-related morbidity and mortality in the absence of viral hepatitis.[2,3] Cross-sec-

tional studies using liver stiffness measurement (LSM) by transient elastography have shown a significant degree of fibrosis among HIV patients, from 17% in one study to a staggering 41% in a recent study that used lower cutoff values of LSM, although both studies involved patients without viral hepatitis.[4,5] Moreover, liver fibrosis progression is accelerated during HIV and HCV co-infection. An analysis using paired liver biopsies showed progression of at least one fibrosis stage (METAVIR) in 34% of HIV/HCV co-infected individuals over a 2.5-year period.[6]

Hepatic fibrosis is a dynamic process initiated by liver injury that results in increased deposition of extracellular matrix proteins in the space of Disse, the area in between the hepatocytes and the liver sinusoids, which is mainly inhabited by hepatic stellate cells (HSCs).[7,8] Accumulation of extracellular matrix proteins and their decreased removal by matrix metalloproteinases results in a progressive replacement of the liver parenchyma by scar tissue, leading to liver fibrosis and its complications.[9] Activation of HSCs is a key event in the process leading to excessive deposition of extracellular matrix proteins and the subsequent fibrosis. This activation of HSCs is triggered by numerous events, such as the release of cellular components by injured hepatocytes, lipid accumulation, the secretion of reactive oxygen species (ROS) produced by macrophages, and exposure to cytokines produced by intrahepatic macrophages, lymphocytes and endothelial cells.[10] In this review, we summarize and comment on the different potential mechanisms and multiple factors related to liver fibrosis during HIV infection (Fig. 1). These include: the effects of antiretroviral therapy (ART), persistent HIV infection-induced immune activation, inflammation due to bacterial translocation from the gastrointestinal tract into the portal circulation, and insulin resistance. We also describe mechanisms related to co-infection with viral hepatitis, but we have not extended on this topic since there are multiple comprehensive reviews about this subject in the literature.[11,12]

Our search strategy included search of the PubMed database from 1980 until 2016. We used multiple search terms, including: HIV, liver fibrosis, inflammation, mitochondrial oxidation, etc. We included primarily research articles, as well as review articles for general relevant and not controversial data.

Metabolic dysfunction during HIV infection

Prior to the availability of effective ART, patients with HIV infection exhibit progressive impairment of their immune systems, leading to AIDS and death. With effective ART, the development of AIDS can be prevented and people with HIV
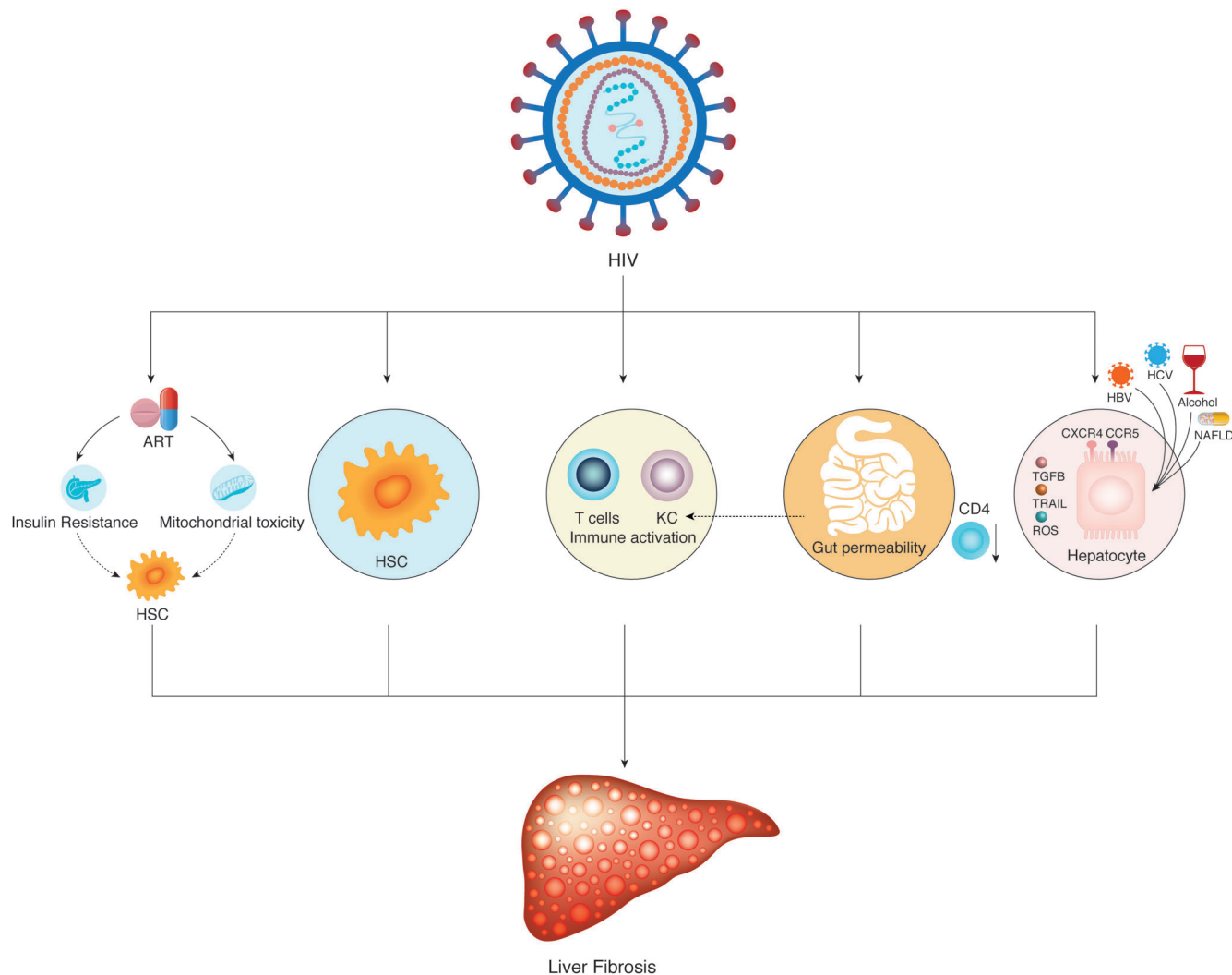
Fig. 1. Factors affecting liver fibrosis during human immunodeficiency virus (HIV) infection. HIV can induce a direct effect on hepatic stellate cells (HSCs), affect T cells and Kupffer cells (KCs), affect hepatocytes through co-receptors, such as CCR5 and CXCR4, and affect mitochondrial DNA. HIV can also increase gut permeability through depletion of intestinal CD4$^+$ cells, increasing bacterial translocation. Antiretroviral therapy (ART) can induce insulin resistance and mitochondrial toxicity in the liver. Other factors like hepatitis B (HBV), hepatitis C (HCV) and alcohol consumption can affect hepatocytes' worsening liver fibrosis.

infection on successful ART have almost the same life expectancy as HIV-uninfected persons (although in countries such as the United States, these elite responders to ART represent less than 50% of the HIV population).[13] As HIV-infected patients age, they develop increased abdominal obesity and exhibit an increased incidence of non-alcoholic fatty liver disease (NAFLD), with 30-40% of HIV-infected patients showing evidence of NAFLD versus 15-20% of HIV-uninfected individuals.[14,15] Moreover, a recent study shows that HIV-positive individuals with NAFLD have almost double the rates of steatohepatitis (lobular inflammation and elevated levels of aspartate aminotransferase/alanine aminotransferase) compared to age/sex-matched HIV-negative controls.[16]

Since excessive lipid accumulation in the liver leads to HSC activation, NAFLD and steatohepatitis enhance the risk of developing liver fibrosis. A study in a Canadian population showed that the mean BMI among HIV-infected patients with liver histology compatible with NAFLD was 26, compared to a mean BMI of 30 among non-infected patients, suggesting that

HIV patients have a lower threshold for developing fatty infiltration of the liver.[17] A cross-sectional study examining hepatic steatosis in HIV patients receiving ART suggested that certain medications included in ART represented independent risk factors for NAFLD and subsequent fibrosis development.[18] However, that study analyzed patients that were already on treatment and did not prospectively address the effect of ART treatment itself on NAFLD.

A recent study by our group that evaluated Hispanics with HIV before starting ART found that 66% of HIV-infected subjects had some degree of fatty liver.[19] In addition, HIV patients can present with HIV-associated lipodystrophy syndrome (HALS). HALS is associated with increased fatty acid deposition in hepatocytes secondary to elevated adiponectin levels associated to lipodystrophy. Also, HALS can lead to insulin resistance, with an increase in plasma glucose.[20] High levels of insulin and glucose eventually stimulate HSC proliferation and increase expression of connective tissue growth factor (CTGF) which promotes liver fibrosis progression.[21,22]

Although the mechanisms are not entirely clear, it seems evident that HIV patients present higher degrees of fat infiltration in the liver in a BMI-related or -unrelated manner, which worsens the direct and immune-related effects of the virus in liver fibrosis.

Role of persistent HIV replication and chronic immune activation

Although ART blocks HIV replication, this effect is not complete and persistent viral replication occurs, even in cases of effective ART outcome.[23,24] HIV does not replicate in hepatocytes, but the HIV co-receptors CXCR4 and CCR5 are expressed on the hepatocyte surface, and the HIV protein gp120 can induce cell signaling in the liver through these co-receptors.[25,26] In hepatocytes, signals triggered through activation of CXCR4 and CCR5 increase expression of pro-collagen alpha-1, a component of type I collagen found in the extracellular matrix that is characteristic of advanced fibrosis. Although the studies that yielded these findings were performed using hepatic cell lines, it is likely that such effects translate to physiologic conditions and contribute to liver fibrosis.[27]

In contrast to hepatocytes, HIV directly infects HSCs, and this infection has been shown to promote HSC collagen I expression and secretion of the proinflammatory chemokine monocyte chemoattractant protein-1 (MCP-1).[28,29] The HIV gp120 protein also induces activation of tissue-inhibitor metalloproteinase (TIMP). The two proteins, MCP-1 and TIMP, are important for chemotaxis of leukocytes, and these mediators promote liver inflammation and fibrogenesis.[28,30] HIV renders hepatocytes sensitive to the TNF-related apoptosis-inducing ligand receptor (TRAIL), which can lead to hepatocyte death and subsequent liver fibrosis.[31,32] HIV can also infect liver macrophages, known as Kupffer cells.[11,33] Although the consequences of HIV expression in Kupffer cells remain unclear, these cells are known to play a key role in hepatocyte apoptosis and to be involved in the induction of steatosis.[34] Moreover, a recent study showed that HIV-infected macrophage/monocytic cells secrete high levels of tumor growth factor-β (TGF-β), which in turn activates HSC to promote fibrosis.[35]

Interestingly, HIV infection leads to a decreased level of IL-17-producing CD4+ T cells, a subset of CD4+ cells involved in liver fibrosis and modulation of HSCs.[36] Moreover, the intrahepatic compartment in patients with chronic HCV contains more IL-17-expressing T cells, and neutrophils represent an important source of IL-17 in the human liver, particularly in late fibrosis stages.[37,38] The interaction between HIV and IL-17 likely plays a role during liver fibrosis, but yet no direct correlation between HIV, IL-17 and liver fibrosis has been exposed.

HIV-specific T cells may also play roles in promoting liver fibrosis, but evaluating intrahepatic virus-specific T cell responses is difficult due to the low frequency of these cells in the liver and limited availability of liver biopsy material from patients.[39] A study performed in HIV/HCV co-infected patients demonstrated the presence of both HCV-specific and HIV-specific T cells in the liver.[40] Interestingly, that study also showed that HIV-specific T cells were more functional than the HCV-specific T cells, and therefore more well equipped to promote HSC activation.

Thus, persistent HIV infection can promote inflammatory processes in the liver that may stimulate the development of fibrosis. The specific interactions of HIV with Kupffer cells, as well as intrahepatic T cell alterations in HIV, deserve further research to better understand their role and potential therapeutic targeting for liver fibrosis.

Microbial translocation and inflammation during HIV infection

In the last decade it has become increasingly clear that microbial translocation is an important determinant of clinical manifestations and disease progression of HIV.[41] Damage to the intestinal mucosa in patients with HIV leads to disruption of the gut epithelial barrier, facilitating leakage of microbial products from the gastrointestinal tract, with bacterial translocation into the portal and systemic circulation.[42] This is thought to be the consequence of virus-induced depletion of CD4+ T cells in the gut and exhaustion of the intestinal macrophage phagocytic function, both of which lead to enterocyte apoptosis and disruption of tight junctions with loss of integrity of the gut mucosa.[43,44]

Increased microbial translocation results in elevated circulating levels of lipopolysaccharide (LPS), LPS-binding protein, soluble CD14 and other mediators, which remain elevated during effective ART.[41,45] When bacterial translocation occurs, Kupffer cells in the liver become activated through toll-like receptor (TLR)4 and other pathogen recognition receptors acting as the first line of defense by clearing bacteria from the liver through phagocytosis. In this process, Kupffer cells are induced to produce cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-1 and IL-6, which are pro-inflammatory mediators that promote liver fibrosis by directly activating HSCs or by priming and recruiting other leukocyte populations.[46,47] Similar to infection of CD4+ T cells, HIV can also directly infect Kupffer cells and promote release of pro-fibrotic mediators.[48] However, one study reported that HIV reduces the number of Kupffer cells in the liver via unknown mechanisms.[49] This HIV-induced loss of Kupffer cells could limit the ability of these cells to directly activate HSCs, but likely leads to higher levels of circulating microbial products, which in turn can affect immune responses, promoting inflammation.

One of the most well-known pro-fibrogenic mediators is TGF-β, which is produced by Kupffer cells in response to TLR ligation upon exposure to microbial compounds.[50] Indeed, many studies have reported a positive correlation between liver fibrosis and serum TGF-β concentrations, intrahepatic TGF-β mRNA levels as well as strong immunohistochemical staining for TGF-β in liver tissue.[51,52] TGF-β directly activates HSC to promote fibrosis, but also plays a homeostatic role to prevent excessive damage by potently suppressing the function of natural killer (NK) cells and T cells, leading to decreased hepatocyte apoptosis and release of HSC-activating mediators.[53] Studies showing a clear impact of bacterial translocation on liver fibrosis have been performed in HIV/HCV co-infected patients.[54] A recent study in HIV mono-infected individuals showed increased levels of soluble CD14 correlating with fibrosis, suggesting activation of monocytes in response to translocation; however, more studies are necessary to further clarify this concept.[5]

Mitochondrial dysfunction and toxicity

HIV itself can induce mitochondrial toxicity. Studies have shown that ART-naïve patients exhibit depletion of mitochondrial DNA in CD8+ as well as B cells, and in CD4+ cells to a

lesser extent (Fig. 2).[55,56] Because these lymphocyte subsets are known to be hyperactivated in persons with chronic HIV infection, it is possible that persistent activation and high cell turnover causes mitochondrial DNA loss. This mitochondrial dysfunction can induce apoptosis in CD4^{+} and CD8^{+} cells and contribute to fat accumulation in the liver with eventual fibrosis.[56,57] Abnormal mitochondrial function induces the production of ROS, which induces oxidative stress with liver injury and decreases beta-oxidation of fatty acids, leading to accumulation of fat in the cytosol.[58] These events are key triggers of NAFLD and steatohepatitis that will lead to the development of liver fibrosis in this setting.[58,59]

Interestingly, adipose tissue of untreated HIV-infected patients shows an increase in mitochondrial DNA content.[55]
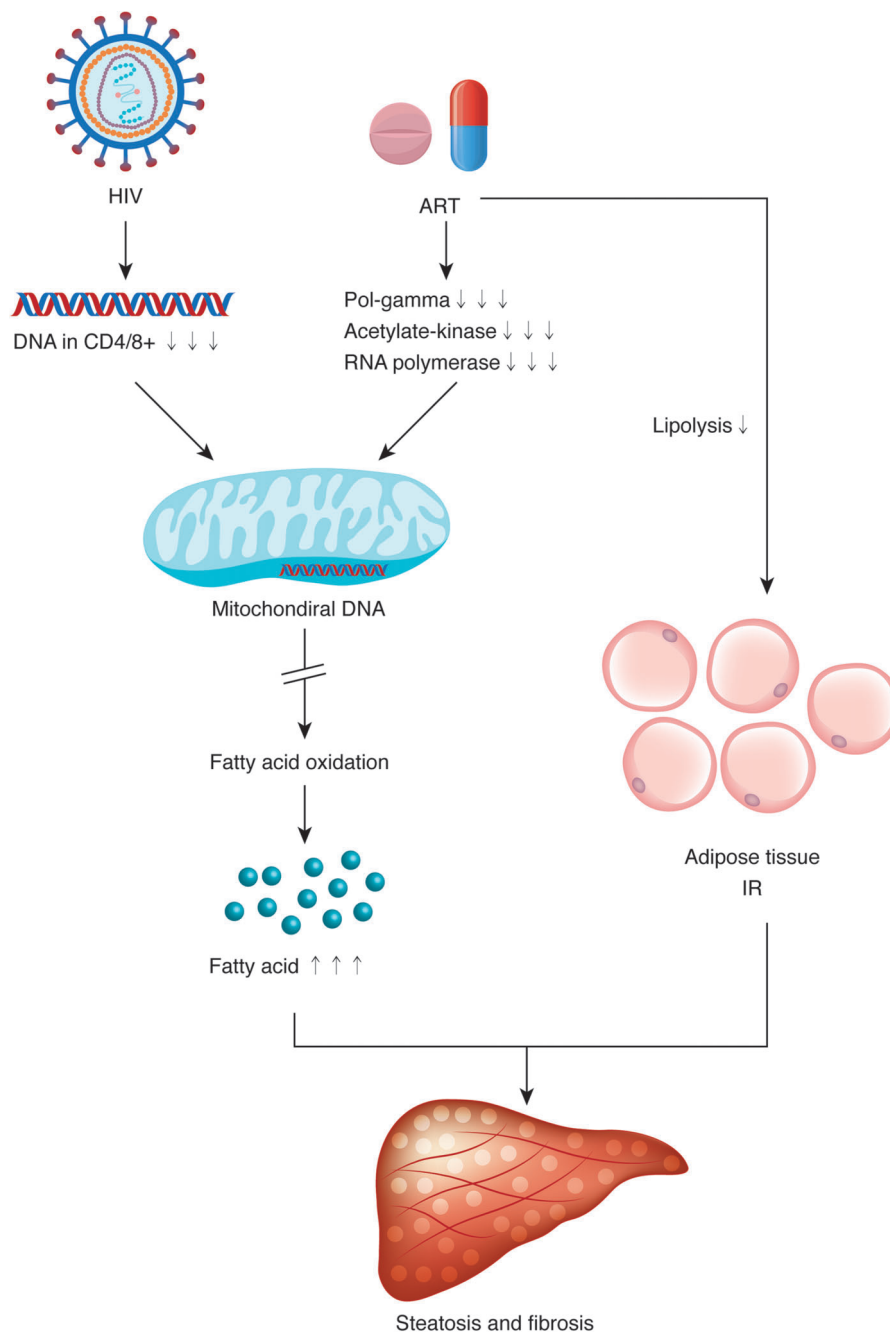

Fig. 2. Effects of human immunodeficiency virus (HIV) and antiretroviral therapy (ART) on mitochondrial toxicity. HIV virus can decrease mitochondrial DNA in CD4^{+} and CD8^{+} T cells. Different ART components can inhibit pol-gamma, acetylate kinase and RNA polymerase related to mitochondria, thereby inhibiting mitochondrial DNA. Decrease in mitochondrial DNA leads to less mitochondria and less beta-oxidation of fatty acids, with an increase in free fatty acids and their deposition in liver parenchyma leading to steatosis. Fat also accumulates in peripheral tissues augmenting insulin resistance (IR), which can also be affected by ART (through inhibition of lipolysis), all of which contributes to steatosis and liver fibrosis.

This could represent a compensatory mechanism to counteract HIV-directed mitochondrial toxicity or HIV-related oxidative stress, but could also alter lipid metabolism and promote fat accumulation in the liver. ART, particularly that with nucleoside reverse transcriptase inhibitors (NRTIs), can directly induce mitochondrial toxicity.[56,59] This is of importance since it is estimated that half of the 35 million people infected with HIV worldwide are on ART.[60] The specific mechanisms by which NRTIs induce mitochondrial toxicity are not entirely clear and differ from drug to drug.[61] However, most NRTIs inhibit pol-gamma, a DNA polymerase critical for the replication of mitochondrial DNA.[59] This inhibition leads to mitochondrial dysfunction due to DNA depletion and microvesicular steatosis.[58]

Other mechanisms unrelated to mitochondrial DNA have been proposed. Some NRTIs, such as stavudine (d4T), can inhibit mitochondrial RNA in cell lines. For d4T, this finding is likely related to its ability to induce stress on the mitochondrial RNA polymerase, which may occur in addition to induction of mitochondrial DNA damage.[62] Zidovudine (AZT) inhibits the mitochondrial adenylate kinase and adenosine nucleotide translocator in isolated mitochondria, both events leading to mitochondrial dysfunction.[61] The majority of studies related to ART and mechanisms of mitochondrial toxicity have been performed *in vitro*, and the most common indicator for toxicity is measurement of mitochondrial DNA that, although generally accepted, is a rather controversial measurement of mitochondrial dysfunction.[63]

Overall, NRTI-containing regimens present the highest risk for liver fibrosis, and no ART regimen is considered completely safe.[60] This is of importance, since although most ART regimens applied in the developed world do not include NRTIs, the great majority of HIV-infected patients are treated in the developing world (such as Africa) with regimens in which NRTIs are part of most first line therapies for ART.[64,65] Interestingly, a recent study suggested that exposure to didanosine (even if later replaced) is a risk factor for liver fibrosis in HIV, although the mechanisms behind this effect are unclear.[66] HIV-infected patients receiving protease inhibitors frequently experience lipodystrophy (known as HALS as described above). Protease inhibitors can decrease peripheral lipolysis through inhibition of GLUT-4 activity, thereby increasing adipocyte size.[67] These hypertrophic adipocytes in the peripheral tissue and abdomen lose functional activity and become resistant to insulin. Consequently, insulin-resistant

adipocytes secrete less adiponectin, which in turn increases body fat, worsening deposition of liver fat and fibrosis.[68] Newer protease inhibitors exhibit less incidence of HALS; however, data is emerging on the direct role of HIV-mediated inflammation promoting endothelial lipase and phospholipase A2 and thus inducing HALS.[69,70]

Finally, some HIV-infected populations have a higher alcohol consumption behavior.[71] It is well known that alcohol is metabolized in the liver, with acetaldehyde promoting glutathione depletion and lipid peroxidation, which leads to mitochondrial damage exacerbating hepatic steatosis and fibrosis.[72] Recent data suggests that alcohol binge drinking can increase bacterial translocation from the gut microbiome.[73] This effect could be exacerbated in HIV-infected individuals, leading to a higher degree of alcoholic steatohepatitis and liver fibrosis. Nonetheless, it remains unclear whether the overall effects of alcohol consumption are accentuated or worsened during HIV infection.[74,75]

Co-infection with viral hepatitis

Approximately 5 million persons are co-infected with HIV and HCV worldwide.[76] Patients co-infected with HIV and HCV experience a more rapid progression to liver fibrosis (Table 1) and develop hepatocellular carcinoma at a younger age than those infected with either virus alone (52 vs. 64 years, respectively).[77–79] While the exact mechanisms for advanced fibrosis in co-infection are not entirely clear, several studies have shed light on this interaction. Both HIV and HCV infection can induce hepatocyte apoptosis via activation of the TRAIL receptors, and increase TRAIL expression by hepatocytes.[32,80] HIV infection renders hepatocytes sensitive to TRAIL with increased TRAIL-R2 expression. It is possible that upon subsequent challenge of the liver with HCV, TRAIL production increases, resulting in hepatocyte death with liver fibrosis.[31]

HCV/HIV co-infected persons also have increased plasma levels of LPS.[81,82] In these co-infected patients with advanced liver disease, bacterial clearance from the liver is impaired, which may establish an enhanced state of intrahepatic inflammation and create an environment for more rapid progression of liver fibrosis.[12,83] Moreover, the HIV gp120 protein can enhance HCV-induced regulation of TGF-β. Besides the pro-fibrinogenic effects described above, TGF-β can also increase HCV RNA replication in cell cultures, which is further enhanced by HIV, suggesting that HIV augments liver

Table 1. Studies addressing liver fibrosis progression in HIV/HCV using biopsies

Name[ref]	Year	N of patients	Findings	Additional comments
Konerman *et al.*[6]	2014	282	Accelerated fibrosis progression	Association with AST/ALT and fibrosis
Leite *et al.*[79]	2015	30	Accelerated fibrosis progression	Association with AST/ALT and fibrosis
Schmid *et al.*[96]	2015	42*	25% experienced fibrosis progression	*N of patients with 2 liver biopsies
Macias *et al.*[83]	2009	135	Fibrosis progression; Decreased progression by ART	Interval between biopsies of 3.2 years
Schiavini *et al.*[78]	2011	58	Reduced fibrosis progression with ART	Correlation between fibrosis and CD4 count
Sterling *et al.*[97]	2010	59*	Similar rate of fibrosis in HIV/HCV than in HCV	*59 HIV/HCV vs 59 HCV; 5-year interval

damage pathways already established by HCV as well as increases HCV RNA replication.[84,85] With the arrival of new direct acting antiviral (DAA) medications for treatment of HCV, it is likely that the fibrinogenic effects related to active HCV replication in HIV-infected patients will be dramatically reduced.[86]

Interestingly, despite the increasing understanding of mechanisms by which HCV and HIV interact to cause liver disease, relatively little is known about viral interactions between HBV and HIV. Moreover, most studies about the natural history of HBV in HIV have been conducted in areas of the world where HBV is acquired in adulthood, leading to the question of whether the effects of HIV are the same when HIV is acquired following establishment of chronic HBV, as occurs in countries with high HBV endemicity.

Approximately 8% of HIV-infected patients are co-infected with HBV, although this rate varies depending on the geographic location. Similar to its interaction with HCV, HIV accelerates the course of liver disease caused by HBV.[87,88] Moreover, HBV patients co-infected with HIV are less likely to become negative for hepatitis B e antigen, increasing the risk of active hepatitis and liver damage compared to cases of HBV mono-infection.[89] LPS levels are elevated in patients co-infected with HBV and HIV, likely predisposing to similar intrahepatic inflammation and fibrosis as seen with HIV/HCV co-infection.[90] Interestingly, HBV has been shown to suppress TLR-mediated innate immune responses, eliciting activation and expression of pro-inflammatory cytokines.[91] This could have implications in the development of liver fibrosis during HIV co-infection, but to date there are no studies addressing this issue.

TGF-β expression has also been associated to liver fibrosis in HBV-infected patients, but a role in HIV co-infected patients has not been demonstrated.[92] Differing from HCV/HIV co-infections, liver fibrosis mediated through apoptosis-related receptors does not seem to play a major role in HBV/HIV co-infection. It has also been hypothesized that HIV modulation of the HBV-specific immune response alters the hepatic cytokine environment, affecting liver fibrosis and disease progression, but this hypothesis has not been thoroughly tested. [93]

Conclusions

With the introduction of ART, a dramatic reduction in HIV-related morbidity and mortality has been observed. However, despite these advances, HIV-infected patients remain at high risk for liver-related disease and mortality.[94–97] The pathophysiology of liver fibrosis in patients with HIV is a multifactorial process. Control of HIV replication will likely mitigate the effects of the virus in liver fibrosis, but mitochondrial toxicity and insulin resistance from the treatment may negatively impact the hepatic environment. In addition, ROS from metabolic disturbances such as alcohol consumption, NAFLD, HBV and HCV infection play a major role in the balance between immune response and fibrosis. Key challenges facing researchers today are to translate our understanding of HIV-mediated liver damage into the development of anti-fibrotic therapies and to identify biomarkers that could allow for individualized approaches to therapy.

Conflict of interest

None

Author contributions

Interpreted studies, wrote majority of the manuscript (JDD), provided guidance in writing, revised the article for important intellectual content (PRB), wrote part of the manuscript, edited content, interpreted studies (AB).

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