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Understanding the Mechanisms of Fibrogenesis in HIV/HCV-Coinfected Patients: Implications for Clinical Practice

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Abstract

HIV/HCV coinfection is associated with accelerated progressive liver disease. Understanding the pathogenesis of liver fibrosis remains crucial to improving the global management of this patient population. This review will mainly focus on the mechanisms involved in the faster progression of liver fibrosis seen in HIV/HCV coinfection, which is caused by a multiplicity of complex factors including virus features, the immune system, interactions between viruses and the immune response, the direct effects of HIV on hepatocytes, fibrinogenetic/inflammatory mediators, microbial translocation, and metabolic abnormalities. The direct role of viruses as well as chronic inflammation, deterioration of immune status, and the harmful effect of antiretroviral agents may all concur to produce dyslipidemia and insulin resistance. Metabolic abnormalities play an important role in the genesis of hepatic steatosis, which is closely linked to liver fibrosis progression. There is also a link between immunologic and metabolic abnormalities: increased expression of leptin and reduced expression of adiponectin seems to be associated with advanced hepatic injury. New antifibrotic strategies are outlined. Ultimately, sustained virological response to hepatitis C therapy is associated with liver fibrosis regression in patients with HIV/HCV coinfection. **(AIDS Rev. 2015;17:159-70)**

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Key words

HIV/HCV coinfection. Liver fibrosis. Pathogenesis. Liver damage.

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Introduction

Since the new directly acting antiviral (DAA) drugs became available a few years ago, HIV/HCV coinfection has become a rapidly changing landscape, and it is now possible to eradicate HCV infection in the majority of patients. The HIV/HCV coinfection is associated with progressive liver disease, and understanding the pathogenesis of liver fibrosis remains crucial to improving the global management of these patients. Liver fibrosis is an important public health concern, with significant morbidity and mortality, and studying the mechanisms of liver fibrosis pathogenesis may allow more effective diagnostic tests and therapeutic targets to be found.

Recent basic and clinical investigations have led to important advances in the knowledge of the pathogenesis of liver fibrosis. One major breakthrough has been the characterization of hepatic stellate cells (HSC) as the main effector cells in liver fibrosis.

In this review, we will discuss the molecular mechanisms involved in the accelerated progression of liver fibrosis seen in patients coinfected with HIV and HCV and its relevance in clinical practice, as well as outlining the main treatment strategies adopted. Ultimately, sustained virological response (SVR) to hepatitis C therapy is associated with liver fibrosis regression in patients with HIV/HCV coinfection.

Outline and methodology

We will conduct our review of the pathogenesis of liver fibrosis in the following order of topics. Firstly, we will outline the role played by HSCs and extracellular matrix. We will then discuss the host-virus interactions that have an additive effect on the progression of liver damage. After this, we will evaluate the practical consequences of liver fibrosis on the course of coinfection; it leads to an acceleration of the disease that can be only partially slowed by the favorable effect of HAART, with curative HCV therapy taking the lead in effectiveness. Finally, we will address the effectiveness of monitoring tools and antifibrotic compounds in liver disease.

We have deliberately excluded the results of clinical trials carried out with DAAs because data on the value of SVR are still inconclusive. The PubMed database were searched for relevant literature using the key words: Bacterial translocation; HIV immunity; HIV/HCV co-infection; Liver fibrosis; Regulatory T cells; HIV; HCV; Liver fibrosis; Cytokines; Microbial translocation; and Matrix metalloproteinases. Literature reviews, conference and workshop abstracts, guidelines, and consensus documents published from 2008 to 2015 were taken into consideration.

The mechanism of fibrogenesis

Fibrosis is a wound-healing response that occurs when there is an imbalance in extracellular matrix (ECM) protein turnover, with enhanced synthesis and reduced degradation. Liver fibrosis can be influenced by toxic, metabolic, and/or viral causes[1]. The development of fibrosis lasts several months to years and is reversible in its initial stages, while the progression of fibrosis can lead to cirrhosis. The point where fibrosis becomes irreversible is incompletely understood and early stages of cirrhosis may be reversible[2].

The role of hepatic stellate cells

A major step in the understanding of hepatic fibrosis was the identification of the cellular sources of the ECM. Although various types of liver cell are involved in hepatic fibrogenesis, the main force driving this process is the HSCs. Located in the Dissé space, HSCs are generally quiescent[3], but once activated they undergo a transition into proliferative, fibrogenic, contractile myofibroblasts. Formerly, HSCs were mainly viewed as “resting cells” that store Vitamin A, impact sinusoidal blood flow, synthesize various ECM components, and trigger the synthesis of erythropoietin and components of the plasminogen-activation system that guarantee homeostasis in the microenvironment of the hepatic sinusoid[3]. However, HSCs have recently been appreciated as having a much broader range of functions, acting as antigen-presenting cells, expressing pattern recognition receptors, responding to damage-associated molecular patterns, and interacting with manifold immune cells to modulate their activity or promote their differentiation (Fig. 1). In response to distinct stimuli, the HSCs activate a complex network of intracellular events. The earliest changes observed during stellate activation result from paracrine stimulation by all neighboring cell types, including sinusoidal endothelium, Kupffer cells, hepatocytes, and platelets[4]. Platelets are another important source of paracrine stimuli such as platelet-derived growth factor (PDGF), transforming growth factor (TGF)-beta-1 and epidermal growth factor (EGF)[4]. The TGF-β1, derived from both paracrine and autocrine sources, is the best characterized and most potent fibrogenic cytokine.

Kupffer cell infiltration and activation also contribute to HSC activation by stimulating matrix synthesis, cell

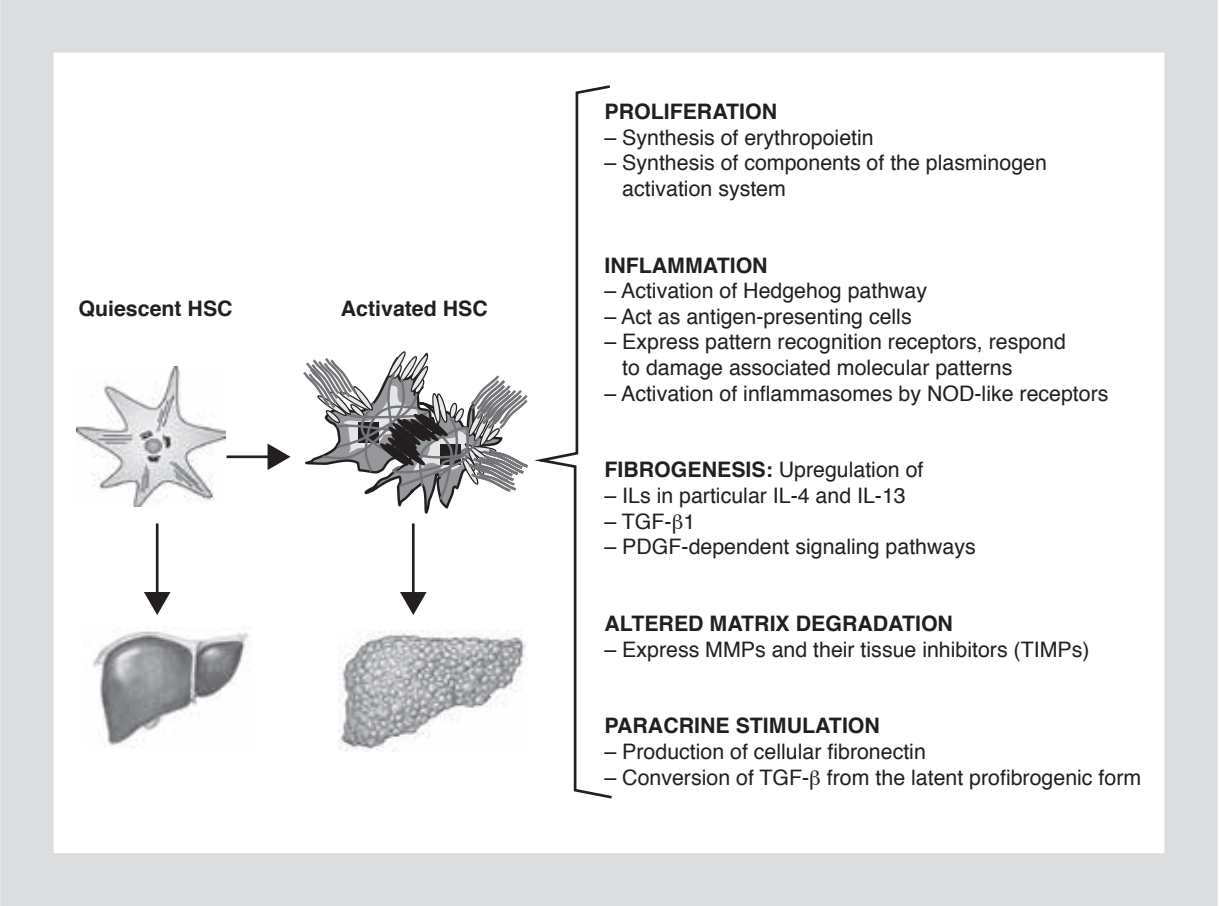

Figure 1. *Role and function of hepatic stellate cells.*
HSC: hepatic stellate cell; NOD: nucleotide-binding oligomerization domain; IL: interleukin; TGF: transforming growth factor; PDGF: platelet-derived growth factor; MMP: matrix metalloproteinase; TIMP tissue inhibitor of matrix metalloproteinase.

proliferation, and release of retinoids by stellate cells through the actions of cytokines (especially TGF-β1) and reactive oxygen intermediates/lipid peroxides (ROS)[4].

Hepatic stellate cells respond to many immunological triggers via toll-like receptors and transduce signals through pathways and mediators traditionally found in immune cells, including the Hedgehog pathway and inflammasome activation. The Hedgehog pathway, known for its regulatory role during embryogenesis[5], can be reactivated during liver injury and induce production of profibrogenic factors such as interleukin 4 (IL-4) and IL-13[5]. The liver is continually exposed to pathogens and commensal bacterial products; for example toll-like receptor (TLR)-4 is the major receptor implicated in signal transduction events induced by lipopolysaccharides (LPS) via the portal vein. Thus, it is not surprising that many liver cells express TLRs[5]. Once activated, the TLRs, which may contribute to persistence of an inflammatory status linked to enhanced fibrogenesis, signal through a complex network of at least two different pathways characterized by different adaptor proteins. These pathways lead to the upregulation of manifold interleukins, which is the hallmark feature of the inflamed microenvironment[6]. Indeed, the balance of cytokine release has an important regulating role on fibrogenesis. Interleukin-17 directly induces the production of collagen expression in HSC via the signal transducer and activator of transcription 3 (STAT3). The significance of IL-22 and its receptors in HSC biology has recently been demonstrated[7]. In HSCs, IL-22 induces senescence through the activation of the STAT3 pathway, SOCS3, p53, and p21, thereby limiting the extent of liver fibrosis and accelerating its resolution[7]. Recent studies show that nucleotide-binding oligomerization domain receptors (NLR), specialized intracellular sensors that trigger the activation of inflammatory caspases which form inflammasome, are expressed in HSCs. Challenge with LPS drastically increases expression of the NLRs in cultured HSCs, suggesting that the activation of inflammasomes

is one additional pathway by which HSCs contribute to liver immunology[8].

In liver immune homeostasis, HSCs generally regulate immunosuppressive responses like the induction of regulatory T-cells (T_{reg}), T-cell apoptosis (via B7-H1, PDL-1) or inhibition of cytotoxic CD8 T-cells. In conditions of liver injury, HSCs act as sensors of altered tissue integrity and initiators of innate immune cell activation by interacting directly with several immune cell subtypes or with soluble mediators. Such interactions include the mutual activation of HSCs and macrophages, or pro-apoptotic signals from natural killer (NK), natural killer T (NKT) and gamma-delta T-cells on activated HSCs.

Extracellular matrix

The ECM consists of a group of macromolecules that provide the structural support of normal and fibrotic liver. These include collagens, non-collagen glycoproteins, matrix-bound growth factors, glycosaminoglycans, proteoglycans, and matricellular proteins. In the normal liver, collagen types I, III, V, and XI are principally found in the capsule, around large vessels, and in the portal triad, while only scattered fibrils containing types I and III collagen can be found in the sub-endothelial space. Smaller amounts of other collagens including types IV, VI, XIV, and XVIII can also be found. Also present are glycoproteins and matricellular proteins including sub-endothelial deposits of fibronectin, laminin, tenascin, secreted protein acidic rich in cysteine (SPARC), and von Willebrand factor[4]. As the liver becomes fibrotic, low-density matrix is replaced with the interstitial type typically seen in wound healing. The liver responds to injury with angiogenic stimulation, with evidence of new blood vessel formation, sinusoidal remodeling, and pericyte amplification[9]. The high-density matrix also activates HSCs, which express the matrix metalloproteinase enzymes (MMP) and their tissue inhibitors (TIMP). Pathological matrix degradation is the early disruption of the matrix in the normal space between hepatocytes and endothelial cells. More importantly, progressive fibrosis is associated with marked increases in TIMP-1[34,35] and TIMP-2[36], leading to a net decrease in protease activity[10].

How HIV/HCV coinfection accelerates fibrogenesis: The role of viruses

Chronic inflammation is the basis of HCV-mediated liver damage[11]. Immunophenotyping of lymphocytes that infiltrate the liver during HCV infection show that they include NK, NKT, T_{reg}, monocytes/macrophages, dendritic cells (DC) and large numbers of $CD4^+$ and $CD8^+$ cells, indicating the involvement of the host immune system in the pathogenesis of liver disease[12-14]. The T-cell response is essential for identification and clearance of HCV, either by cytolysis of virus-infected cells or non-cytolytic clearance via cytokine- or chemokine-mediated effects. A greater T-cell response (both virus-specific $CD4^+$ and $CD8^+$ cells) during acute, rather than chronic, HCV has been reported[15], and a strong influence of chemokine-chemokine receptor interactions on the recruitment of T-cells to sites of inflammation in the liver during chronic HCV infection has been well documented. Genetic studies have found that polymorphisms in the HLA class I and class II molecules on chromosome 6, which are linked to CD8 and CD4 responses, respectively, are associated with spontaneous HCV clearance, thereby confirming the importance of T-cells in the elimination of HCV infection[15]. Expression of intrahepatic chemokine ligands and their receptors has been associated with severe HCV-induced liver inflammation. The release of inflammatory cytokines and chemokines is induced by the crosstalk between HSCs and HCV-infected hepatocytes[16]. It is likely that inflammatory cell activation is triggered by HCV core and NS3 proteins inducing IL-1 receptor-associated kinase activity through TLR-2. The HCV-associated interleukin receptor-associated kinase activation may also contribute to the induction of cytokines and chemokines by HSCs. The expression of chemokine receptor type 5 (CCR5) on activated T-cells relies upon their recruitment to the liver[16]. Indeed, intrahepatic expression of the ligands for CCR5 (RANTES, MIP-1β, and MIP-1α), which have been linked to a high grade of liver inflammation[16], is elevated in HCV-infected patients. Chronic HCV infection is also known to be associated with increased levels of TNF-α in the liver and serum of patients. Considering that TNF-α elevation may interfere with insulin signaling[17], this cytokine could be the key molecular link between inflammation, steatosis, and fibrosis in chronic HCV infection. The HCV infection also promotes the activation of macrophages, in particular Kupffer cells, which release ROS and large amounts of proinflammatory and fibrogenic mediators such as TGF-β1[18].

Mechanisms of liver fibrosis progression in patients with HIV/HCV coinfection

Several epidemiological and clinical findings indicate a direct role of HIV in inducing liver fibrogenesis and emphasize the impact of HIV in the induction of accelerated liver damage, even in patients with no concomitant

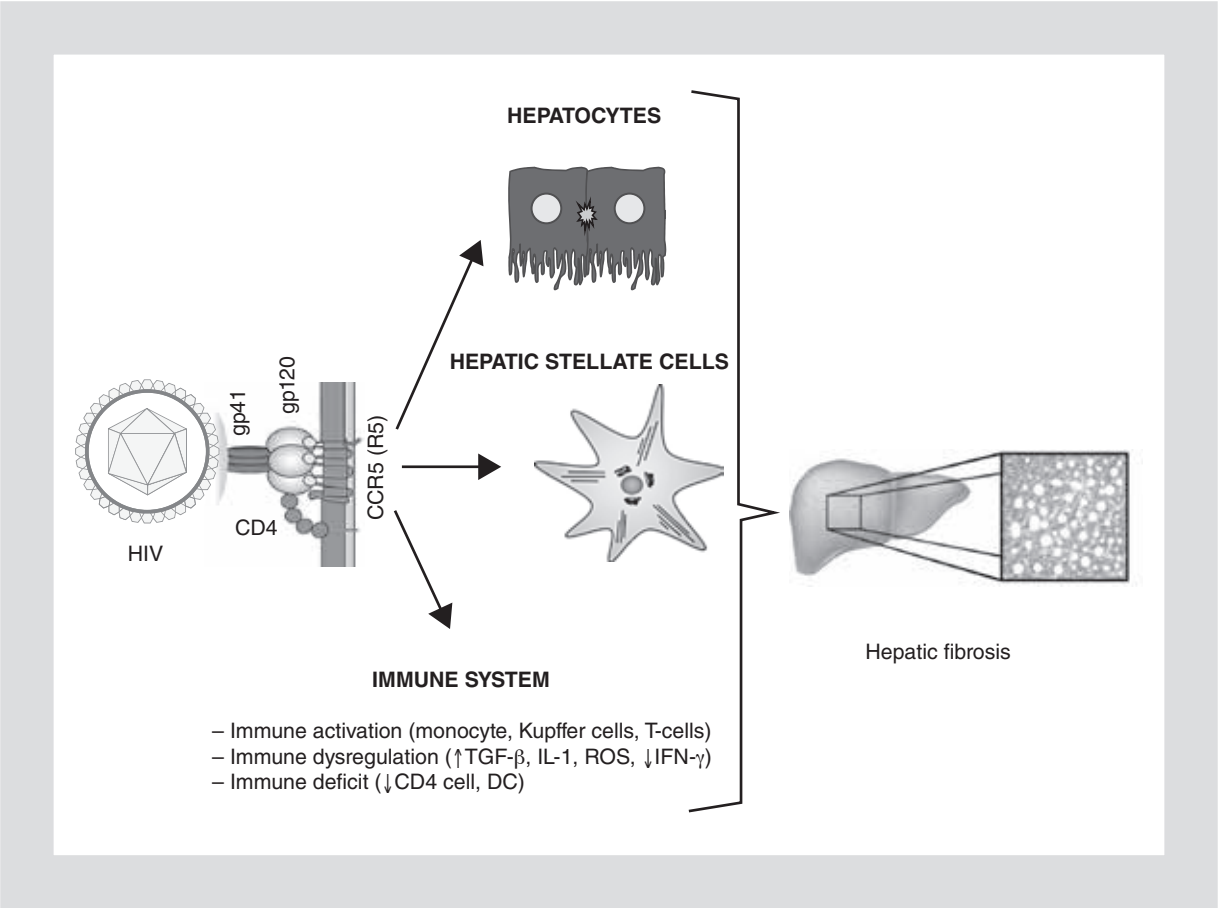

Figure 2. *Interaction between HIV and hepatic stellate cells leading to accelerated fibrosis.*
IL: interleukin; TGF: transforming growth factor; ROS: reactive oxygen species; IFN: interferon; DC: dendritic cell.

viral hepatitis coinfection. In a large North American study on four groups of women (HCV-monoinfected, HIV-monoinfected, HIV/HCV-coinfected and HIV-seronegative/HCV-seronegative women), HIV RNA plasma levels were associated with increased FIB-4 score in the absence of HBV, HCV, HAART or alcohol use[19]. Using transient liver elastography (TE), liver damage has been frequently detected in HIV-monoinfected patients and correlated with high plasma HIV RNA levels[20,21]. Indeed, hepatocytes (and other resident liver cells) are known to express key HIV coreceptors, including CCR5 and chemokine receptor type 4 (CXCR4), and HIV itself has a direct cytopathic effect on hepatocytes. A productive HIV infection was demonstrated in hepatocytes through identification of hepatotropic variants of HIV in autopsied liver tissues, and more recently in HSC, by detection of p24 antigen and HIV RNA[8]. Both HIV and its envelope protein glycoprotein 120 (gp120) have been shown to induce cell signaling in the liver through interactions with the CCR5 and CXCR4 expressed on the surface of hepatocytes, HSCs, and other immune cells[22,23]. This effect of HIV and gp120 on HCV replication is blocked by antibodies for CCR5 or CXCR4, indicating that CXCR4 or CCR5 coreceptor engagement by HIV is essential for stimulation of HCV replication. The effect of HIV on HCV replication is also blocked by a neutralizing antibody to TGF-β1, one more indicator that HIV itself could directly contribute to hepatic fibrosis and increased HCV replication in a TGF-β1-dependent manner. Transcripts for the chemokine receptors CCR5 and CXCR4 (which bind gp120) are detectable in human HSCs[23]. It has therefore been speculated that gp120 may induce HSC accumulation through direct chemotaxis and secretion of monocyte chemoattractant protein-1 (MCP-1) by HSCs themselves, and by activated macrophages[23,24] (Fig. 2).

Immunological abnormalities and inflammatory mechanisms

The quantitative and qualitative impairment of T-cell responses associated with HIV infection may have a

negative impact on HCV disease progression. The HIV-induced CD4 depletion is independently associated with the severity of liver fibrosis in chronic HCV infection. A recent study has demonstrated that both HIV-induced loss of CD4+ T-cells and dysregulated CD4+ T-cell function lead to a reduction in the antifibrotic activity of NK cells[25]. In addition, marked intrahepatic CD4 T-cell depletion, associated with an increase in apoptotic lymphocytes in the liver lobule, has been demonstrated in HIV/HCV-coinfected patients. Regulatory CD4+ T-cells are a subset of CD4+ T lymphocytes that express CD25 (IL-2 receptor a-chain) on their surface[25,26]. In HCV infection, T_{regs} have been associated with impairment of peripheral blood immune responses and associated with HCV chronicity[27]. The HCV patients have higher levels of T_{reg} suppressive activity in blood compared to healthy controls. *Ex vivo* studies on hepatic tissue demonstrate that CD4+FOXP3+ cells are the main intrahepatic T_{reg} population in HCV-infected patients, and that FOXP3 activity is inversely proportional to hepatic fibrosis in chronically infected patients. Several studies describe changes in the frequency of circulating T_{regs} in HIV infection, noting that they increase as a relative proportion of CD4+ T-cells, but decline as CD4+ declines.

HIV might preferentially destroy or inactivate T_{regs}, which then leads to excessive immune activation. The number of hepatic FOXP3+ cells in the periportal tract has been found to be significantly lower in HIV/HCV-coinfected patients than in HCV-monoinfected individuals[28]. The vast majority of FOXP3+ T-cells in infiltrates from these patients are CD4+ T-cells, which indicates a lower number of T_{regs} in coinfection. This population may exhibit a lower level of regulatory activity. The altered balance between CD4 and CD8 response in HIV infection may be due to a profound dysregulation of the peripheral and intrahepatic cytokine networks, which contributes to the accelerated course of liver fibrosis. Another pathway by which reduced CD4 cell counts promote hepatic fibrosis is a reduction in the secretion of T-helper 1 (Th1) cytokine interferon (IFN)-γ, a well known antifibrotic cytokine. The increased Th2 response seen in HIV infection is associated with secretion of Th2 cytokines (IL-4, IL-5, IL-10, and IL-13), which are known to play a profibrotic role. As mentioned above, an important mediator of liver fibrogenesis is the cytokine TGF-β1, and significant increases in TGF-β1 expression have been reported in the liver and serum of patients with HIV/HCV coinfection. Both HIV/HCV-coinfected and HCV-monoinfected patients exhibit significantly higher levels of circulating TGF-1 compared with healthy controls, with no significant differences between the three groups of patients. Interestingly, this increase was particularly pronounced in the HIV/HCV-coinfected group with detectable plasma HIV RNA, which supports the idea that TGF-β1 is upregulated by HIV. An inverse correlation between the level of TGF-β1 and liver stiffness level has also been found, even if TGF-β1 is known to be a profibrotic cytokine[28,29]. Another cytokine associated with liver inflammation and immune regulatory pathways in the liver parenchyma is IFN-γ-inducible protein 10 (IP-10)[30]. This IP-10 is a chemokine that binds to the CXCR3 immune system receptor present on a number of cells, including monocytes, NK cells, and T-cells. Nevertheless, it has recently been suggested that the regulatory protein HIV tat is able to induce IP-10 expression and subsequently increases the replication of HCV and HCV/HIV in coinfected individuals[31]. Dysregulation of IL-1 may also play a role in maintaining the HSCs in the proliferative state responsible for hepatic fibrogenesis in HIV/HCV coinfection. Indeed, several viruses are able to activate caspase-1 and induce IL-1β production through inflammasome signaling, highlighting the potential role of inflammasomes in the immune response to viruses[32]. Moreover, HCV products induce intracellular ROS and ion flux, both of which trigger the NLRP3 inflammasome during virus infection. Finally, the HCV p7 protein is a transmembrane cation channel that also drives ion flux, and is thereby also a potential mediator of NLRP3 inflammasome activation during HCV infection[33]. Indeed, high levels of IL-1β have been observed in patients from the early stages of HIV infection, suggesting a role of NLRP3 inflammasome in driving the inflammatory response and subsequent liver fibrosis[34]. Finally, recent studies have highlighted the impact of IL-6 levels on liver fibrosis in HIV/HCV-coinfected patients. Interleukin-6 is secreted by T-cells and macrophages in response to microbial products and other stimuli, and it represents a marker of systemic immune activation and liver inflammation. High circulating levels of IL-6 are associated with portal hypertension and decompensated liver cirrhosis in both HIV-infected and -uninfected patients[35].

Microbial translocation in HIV/HCV coinfection

The central role of immune activation in the pathogenesis and progression of HIV disease has been highlighted by both animal and human studies, con-

firming that the major driving force behind chronic immune activation is the translocation of microbial products from the damaged gastrointestinal tract to the portal and systemic circulation. Microbial translocation in the host with severe liver fibrosis leads to reduced clearance of bacterial products and increased immune activation. During HIV infection, the massive depletion of CD4 T-cells in the intestine leads to an alteration of the immune component of the surface of the gastrointestinal mucosa that can induce greater translocation of LPS[36]. Increased levels of circulating LPS have been shown during HIV infection, suggesting greater immune activation and a consequent progression of the disease alongside $CD4^+$ T-cell depletion. Also, LPS raises levels of macrophage activation marker sCD14, also considered an indicator of inflammation[36]. Soluble CD14 and LPS are undoubtedly important indicators of liver disease progression in HIV/HCV-coinfected persons[36]. It has been shown that LPS accelerates liver fibrosis through engagement of TLR-4 on hepatocytes and HSCs following membrane binding via LPS-binding protein and CD14. These events lead to simultaneous TGF-β1 stimulation through a nuclear factor kappa B (NF-κB)-dependent pathway and Kupffer cell activation, which, in turn, induces the generation of superoxide and the release of proinflammatory and profibrogenic cytokines such as TNF-α, IL-1, IL-6, and IL-12, all of which induce liver damage. Soluble CD14 levels have been found to be independently associated with a decreased risk of liver disease progression or liver-related death, because sCD14 prevents the interaction of LPS with membrane-bound CD14 on the surface of phagocytes, impeding their inflammatory response[37].

Dysregulation of matrix metalloproteinases and the role of fibrosis biomarkers

In HIV/HCV-coinfected patients, there is a striking increase in circulating TIMP-1 levels, more evident in subjects with advanced CD4 depletion. On the other hand, there is no increase in the plasma concentrations of MMP-9, suggesting an imbalance between circulating TIMP-1 and MMP-9 during HIV infection[10]. It is possible that this altered balance may play a potential role in exacerbating the progression of liver fibrosis in HIV patients coinfected with HCV. Cytokines such as TNF-α, TGF-β, IL-1, and IL-6 are involved in the expression pattern of both MMPs and TIMPs. It is conceivable that the cytokine dysregulation documented in HIV contributes to the activation of HSCs and the upregulation of TIMPs[10].

Influence of metabolic factors on liver fibrosis

Metabolic alterations are common during HIV/HCV coinfection and play an important role in the genesis of hepatic steatosis, which is closely related to liver fibrosis progression[38]. These alterations, including dyslipidemia and insulin resistance, are directly due to the virus, as are chronic inflammation, deterioration of immunological status, and toxic exposure to antiretroviral therapy. Both HIV itself and the antiretrovirals promote the development of insulin resistance and the abnormal deposition of fatty acids in hepatocytes through mitochondrial dysfunction. Insulin resistance itself may play a key role in the pathogenesis of so-called virus-associated fatty liver disease, which in turn leads to liver steatosis and inflammation[39]. Furthermore, high levels of insulin and glucose stimulate HSC proliferation and increase the expression of connective tissue growth factor. Emerging evidence suggests that there is a link between immunological and metabolic perturbations. In particular, the increased production of proinflammatory cytokines and perturbance in adipokines (including adiponectin, leptin, resistin, and visfatin) recognized in HIV/HCV-coinfected patients may have an effect on insulin resistance, promoting metabolic syndrome[40,41]. Low levels of adiponectin may induce hepatic and systemic inflammation, which could lead to increased expression of resistin and leptin. Several studies have shown that resistin and leptin have a profibrogenic and proinflammatory role. Resistin causes expression of proinflammatory chemokines and IL-8, induces activation of transcription factor NF-κB, and has proinflammatory actions on HSCs. Leptin mediates HSC activation and liver fibrosis through indirect effects on Kupffer cells, partially mediated by TGF-β1[42].

The role of alcohol and drug use in liver fibrosis

Most HIV/HCV-coinfected individuals, at least in the developed world, are former or active intravenous injection drug users (IDU). In addition to heroin, other substances, such as cannabis, amphetamines, and cocaine, cause liver injury and fibrosis progression[43]. Amphetamines have an extensive hepatic metabolism and the generation of a toxic metabolite may be the cause of hepatic injury[44]. Cocaine can lead to a range of liver abnormalities, and its metabolites are involved

in oxidative stress and lipid peroxidation in hepatocytes[45]. Among HIV/HCV-coinfected IDUs there is a high prevalence of heavy alcohol use, which plays a potential role in faster liver disease progression. Indeed, alcohol is metabolized in the liver and promotes glutathione depletion and lipid peroxidation, leading to mitochondrial damage and local lymphocyte recruitment[46]. Furthermore, acetaldehyde plays a central role in fibrogenesis by increasing the expression of collagen during HSC activation. Alcohol may also inhibit the antifibrotic action of NK cells and it increases gut permeability and translocation of bacterial products such as LPS, which in turn triggers liver fibrogenesis[46].

Clinical course of liver disease in coinfected patients

In the current HAART era, liver disease caused by chronic HCV infection has now become an increasingly important cause of morbidity and mortality among HIV-infected patients in the developed world, where the once-typical severe opportunistic immunodeficiency infections have declined considerably. It is well established that HIV coinfection accelerates progression to clinical HCV-related liver outcomes, and that this effect might be attenuated by HIV suppression[47].

Infection with HCV is not associated with an increased rate of AIDS-defining events or deaths, but coinfected patients might have lower $CD4^+$ T-cell counts compared with HIV-monoinfected patients. HCV coinfection dramatically promotes the development of hepatocellular carcinoma (fivefold) and of cirrhosis (10- to 20-fold). Coinfected patients also develop hepatocellular carcinoma at a younger age and with more liver-related complications at presentation than HCV-monoinfected patients[47].

Influence of antiretroviral drugs on liver fibrosis

In coinfected patients, HAART should be started as soon as possible because antiretroviral initiation is associated with a delay of cirrhosis progression. Patients with undetectable HIV RNA show a slower progression of cirrhosis than those with detectable viremia[47]. Treatment of HIV is also associated with reduced complications from end-stage liver disease, including hepatocellular carcinoma and death. Antiretroviral therapy (ART) initiation is recommended for all coinfected patients, regardless of $CD4^+$ T-cell count[48]. However, other variables need to be taken into account in patient management. First, coinfected patients receiving both HIV and HCV treatment have a higher pill burden and thus an increased risk of drug-drug interactions and drug-induced liver injury, particularly those with advanced liver disease. To avoid or reduce the potential for drug toxicity and interactions, HIV treatment might be deferred and HCV treated first in antiretroviral-naive coinfected patients with CD4 counts > 500 cells/µl. Drug-drug interaction has become less of an issue, however, with the advent of HIV integrase inhibitors such as raltegravir and dolutegravir, which exhibit relatively few interactions, especially when compared to protease inhibitors or non-nucleoside reverse transcriptase inhibitors.

Nevertheless, the use of some antiretrovirals might preclude the use of some direct-acting HCV antiviral agents, particularly those targeting the HCV protease, because of drug interactions mediated by the cytochrome p450 pathway[48].

HAART may reduce the risk of HCV-associated hepatic decompensation by controlling HIV-mediated immune dysfunction and dysregulation through CD4 recovery[47]. This hypothetical mechanism is consistent with prior studies suggesting that CD4 count gains and suppression of HIV replication are associated with reduced rates of advanced hepatic fibrosis, cirrhosis, hepatic decompensation, and/or death[47]. On the other hand, immune reconstitution could exacerbate host-mediated hepatic inflammation and chronic antiretroviral-associated hepatotoxicity, increasing the risk of hepatic decompensation. Whether HAART has an ultimately positive effect on liver-related outcomes is as yet unclear because the only assessment of the direct impact of HAART on liver necroinflammatory activity suffered from a cross-sectional design using liver biopsies and did not evaluate hard clinical liver disease progression events. Drug-induced liver injury associated with HAART is uncommon in patients with HIV/HCV coinfection, whether or not they have advanced liver fibrosis. In one subgroup of Chou, et al. study, liver fibrosis improved after receiving HAART. In addition, preexisting advanced liver fibrosis did not influence the development of transaminase elevations[49].

In a study evaluating the impact of HAART on liver stiffness, the authors showed a significant association between longer duration of HAART and a decrease in, or stabilization of, hepatic fibrosis in HIV/HCV-coinfected patients, suggesting a beneficial effect. In agreement, liver fibrosis progressed more slowly in HIV/HCV-coinfected patients receiving long-term HAART, akin to what has been seen in HCV monoinfection[50,51]. In a

cross-sectional study, a negative effect on liver fibrosis of some antiretroviral nucleoside agents, particularly didanosine, was observed. This was probably due to the high mitochondrial hepatotoxicity of this agent[50]. Didanosine is no longer recommended as HIV therapy and safer antiretroviral drugs should be used in the management of HIV/HCV-coinfection to exploit the protective effect of HAART on liver fibrosis.

An increased risk of liver fibrosis progression in HIV/HCV-coinfected patients following HAART interruption has been reported, again suggesting a link between HAART intake and fibrosis progression. HAART may also lead to development of acute toxic hepatitis, steatosis, steatohepatitis, liver fibrosis, and non-cirrhotic portal hypertension, counteracting any potential benefits of immune reconstitution. The mechanisms involved in HAART-associated hepatotoxicity include mitochondrial toxicity, steatosis, and release of inflammatory cytokines such as TNF-α, IL-6, and IL-1β. All of these data support the need to improve HCV treatment and initiate HAART early in HIV/HCV-coinfected patients.

New tools for assessing liver fibrosis progression

Although significant progress has been made, several challenges remain to optimize the management of HIV/HCV-coinfected patients. These challenges include improving the rate of treatment uptake and retention in care; developing a scoring system for the prioritization of treatment; and minimizing potential drug interactions between HCV and HIV agents. Some of these challenges have been attenuated by the availability of new DAAs, but others remain unsolved[52]. Every patient coinfected with HCV and HIV should first be considered for therapy for both infections, and undergo an initial assessment of fibrosis. Several noninvasive scoring systems have been tested among HCV-monoinfected patients. The aspartate aminotransferase:platelet ratio index (APRI), FIB-4, and the Forns index are accurate for diagnosis of cirrhosis but not for splitting out stages F2-F4. Algorithms combining noninvasive tests, such as TE and FibroTest (FT) or FT and APRI (SAFE), have been proposed to improve diagnostic accuracy in HCV-monoinfected patients[52]. However, no information is available on the performance of such algorithms in HIV/HCV-coinfected patients, in whom their performance could be suboptimal.

The performance of the major non-invasive tests for staging liver fibrosis in HIV/HCV-coinfected patients has been compared recently. The TE, FT, the APRI and two algorithms combining TE and FT or APRI and FT were evaluated. A total of 116 HIV/HCV-coinfected patients with various stages of liver fibrosis were examined. The sensitivity and specificity of non-invasive tests for predicting liver fibrosis or cirrhosis was tested by means of ROC curves. Both TE and FT had a similar diagnostic accuracy for significant fibrosis, whereas for cirrhosis, TE displayed the best accuracy. The use of the algorithms combining tests did not improve the diagnostic performance. The importance of such strategies is that they may eventually spare the need for a liver biopsy[52].

In a large multivariate analysis[53], TE performed better than any other serum fibrosis biomarker indexes for detecting advanced fibrosis and cirrhosis in HIV/HCV-coinfected patients, although some confounding factors may preclude its wider acceptance, such as misclassification due to steatosis and the difficulty in defining optimal cut-offs. The APRI is primarily helpful for excluding significant liver fibrosis. Both FIB-4 and Forns remain attractive because they are cheap and include widely available markers. While performance of panels such as HGM-3 or Fibrometer has been superior in some studies, they require some non-routine parameters that are expensive and not widely available. Furthermore, they require additional external validation before conclusions can be made about their predictive accuracy.

The rate and distribution of liver fibrosis stages and risk factors is poorly characterized in HIV-monoinfected individuals. The FIB-4 and APRI should be used to identify patients at risk for developing liver fibrosis and need for further clinical work-up. Tools for fibrosis assessment based on markers of ECM production have recently been proposed. During progression of liver fibrosis, both the synthesis and degradation of ECM increase[54,55]. Endopeptidases, such as MMP-2 and MMP-9, are enhanced during ECM remodeling, especially in HIV-positive patients[56-58]. During the synthesis and degradation of collagen by MMPs, small fragments are released into the circulation, and their levels reflect the degree of liver dysfunction and portal hypertension in patients with alcoholic cirrhosis[55]. The evaluation of circulating collagen fragments as biomarkers for liver fibrosis staging and portal hypertension has been examined in HIV/HCV-coinfected patients, using FibroScan and FIB4 as comparators. Serum PRO-C3 (true collagen type III formation) levels may serve as biomarkers for the extent of liver fibrosis, liver injury, and portal hypertension in HIV/HCV-coinfected patients. Additional markers of ECM remodeling such as

serum C4M and C5M levels might be more useful for the diagnosis of portal hypertension.

Host genetic factors may play an important role in fibrosis progression. A genome-wide study performed on HCV-monoinfected patients showed that a combination of seven single nucleotide polymorphisms in a cirrhosis risk score was able to predict progression to advanced fibrosis/cirrhosis. The study showed for the first time that there was a relationship between cirrhosis risk score and liver fibrosis progression in HIV/HCV-coinfected patients. The cirrhosis risk score helped to discriminate between nonprogressor (F0) and progressor patients (F1/F2/ F3/F4). However, the cirrhosis risk score seems to be less useful in HIV/HCV-coinfected patients than in HCV-monoinfected patients. Indeed, the authors observed that the cirrhosis risk score is able to predict fibrosis progression in patients with HCV genotype 1/4. However, no significant results were obtained for HCV genotype 2/3, which may be because of the reduced number of HCV genotype 2/3 patients that do not have liver fibrosis. On its own, the cirrhosis risk score thus seems not to have much value for identifying HIV/HCV-coinfected patients who are at high risk of developing liver fibrosis. However, this score, coupled with clinical factors (age at HCV infection, IDU, gender, IL-28B, and HCV genotype), might help to distinguish between non-progressors and progressors. Due to its potential role in HIV-associated immunopathology, MMP enzyme activity might constitute a novel therapeutic target in HIV infection. As for fibrosis markers, some studies on patients infected with HCV report that hyaluronic acid is an accurate indicator of fibrosis and predictor of individual hepatic complications. Hyaluronic acid is a biomarker present in the extracellular matrix that is eliminated from the bloodstream by the liver sinusoids. High CD4 counts in patients with HIV/HCV coinfection have been associated with a reduced risk of substantial increases in hyaluronic acid levels and hepatic fibrosis. Indeed, patients with low and stable plasma hyaluronic acid levels have a very low risk of liver disease progression. Hyaluronic acid is also a strong predictor of later development of hepatic encephalopathy or liver-related death in HIV-1/HCV coinfection, and a higher annual increase in hyaluronic acid has been reported in patients experiencing liver-related events during follow-up, as compared with those who did not. Hence, hyaluronic acid plasma detection, alone or in combination with other non-invasive methods, may be a useful means of monitoring the progression of liver disease and predicting the risk of hepatic complications in HIV/HCV-coinfected patients[10].

New antifibrotic drugs

Based on the expanded knowledge of liver fibrosis pathogenesis, attention has now been directed towards antifibrotic therapies. This is an area that remains to be conquered by drug development, where potential benefits and risks are both enormous. Hepatoprotectants, which are not truly antifibrotic agents, are a group of molecules developed to minimize the release of damage signals from injured epithelial cells that drive inflammation and fibrosis. Emricasan, a molecule that blocks apoptosis of hepatocytes, is currently being tested in clinical trials for several liver-related conditions. Similarly, the inhibition of cathepsin-B attenuates liver injury in experimental models. Antioxidant therapy may also exert a preventive effect on hepatocyte injury. A second approach against liver fibrosis progression is based on drugs with direct antifibrotic activity. The discovery of membrane and nuclear receptors expressed by HSCs has opened new possibilities for antifibrotic therapies. Blocking the renin/angiotensin system by angiotensin-converting enzyme inhibitors or AT1 receptor blockers may be an effective strategy to treat liver fibrosis and is currently being tested in human trials[59]. Initial trials of the blockade of endothelin-1 type A receptor, which in rodents is antifibrotic and also improves portal hypertension, have been discouraging, at least regarding first generation human endothelin-1 receptor antagonists, due to hepatotoxicity.

Cannabinoids also remain an attractive possibility for modulating hepatic fibrosis[59]. Mediators of tyrosine kinase receptors such as PDGF, FGF, and TGF are also appealing. Peroxisome proliferator-activated receptor agonists reduce collagen expression and HSC activation *in vitro*, although these effects have not been reproduced in clinical trials. TGF-β1 is the most potent stimulus to the synthesis of collagen I and other matrix constituents, and thus inhibiting its actions remains a major focus of antifibrotic efforts in the liver.

Enhancement of ECM degradation is another potential antifibrotic strategy, in particular by stimulation of TIMPs. The apoptotic activity of HSCs reflects a balance between apoptotic stimulation and survival signals, which can be manipulated therapeutically. For example, inhibition of NF-kB by gliotoxin[59] was found to accelerate recovery from fibrosis in an animal model. The use of bone marrow progenitor cells to promote regeneration and enhance matrix degradation is an intriguing and somewhat controversial new approach to antifibrotic therapy. Nevertheless, the best anti-fibrotic therapy is elimination of the underlying disease process[60].

Conclusions

Although significant advances in knowledge of the pathogenesis of liver disease in HIV/HCV-coinfected patients have been achieved over the past few years, the mechanisms involved in the accelerated progression of hepatic fibrosis in this population remain largely unsolved. A complex and multifactorial interplay of viral factors, the immune system, their interactions, direct effects of HIV on hepatocytes, fibrinogenetic/inflammatory mediators, microbial translocation, and metabolic abnormalities are involved. The types of lymphocytes that infiltrate the liver during HCV infection include NKT, T_{reg}, monocytes/macrophages, DC, and numerous $CD4^+$ and $CD8^+$ T-cells. The latter are essential for the recognition and clearance of HCV, either by cytolysis of virus-infected cells or by non-cytolytic clearance by cytokine or chemokine-mediated effects.

The interaction between HSC and hepatocytes plays an important role in this pathogenetic mechanism. Likewise, the interplay between the host immune system and HIV, the depletion of $CD4^+$ T lymphocytes, and the dysregulation of peripheral and intrahepatic cytokine networks is largely responsible. The prevalence of secretion of Th2 cytokines (IL-4, IL-5, IL-10, and IL-13) results in a pro-fibrotic state that favors liver fibrosis. The secretion of TGF-β and the decreased activity of regulatory T-cells also results in a paradoxical and persistent immune activation with increased inflammatory responses that are not as pronounced as in HCV-monoinfected patients.

The expression on hepatocytes (and other resident liver cells) of key HIV coreceptors, including CCR5 and CXCR4, and the interaction of gp120 and HSC, may cause an ever increasing vicious cycle characterized by increased apoptosis of hepatocytes, activation of HSC with production of proinflammatory and profibrotic cytokines, and dysregulation of metalloprotease and collagen deposition. Furthermore, the massive depletion of $CD4^+$ T-cells in the intestine during primary HIV infection may lead to disruption of immune responses on the gastrointestinal mucosa that can promote further microbial translocation. This results in increased levels of circulating LPS, massive activation of the immune system with increased expression of the macrophage activation marker sCD14, and progression of liver damage by stimulation of HSCs and production of pro-fibrotic cytokines like TGF-β1.

The direct role of the viruses as well as chronic inflammation, deterioration of the immune system, and the toxic effects of some antiretroviral agents may all concur in the onset of dyslipidemia and insulin resistance that play an important role in the genesis of hepatic steatosis, which in turn contributes to liver fibrosis progression in coinfected patients. A link between immunological and metabolic abnormalities has been demonstrated, characterized by increased expression of leptin and decreased expression of adiponectin, both of which are associated with advanced hepatic disease.

Given that sustained virological response to hepatitis C therapy is associated with regression of liver fibrosis in patients coinfected with HIV and HCV, new DAA therapies must be prioritized in this population, historically considered as difficult to treat and cure. The main challenges in patient management include improvements in diagnosis and in treatment rates and avoidance of drug interactions. Accurate assessment of liver fibrosis staging is key for assessing prognosis and prioritization of treatment in HIV/HCV-coinfected patients. Although several serum biomarkers indexes (APRI, FT, FIB-4) and TE have been used for staging liver fibrosis in cross-sectional analyses, longitudinal studies may provide a unique opportunity for better understanding the dynamics of liver fibrosis progression in this population.

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