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Mechanisms of Accelerated Liver Fibrosis in HIV-HCV Coinfection

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Abstract

Although there is evidence that hepatitis C virus (HCV) progresses rapidly in HIV/HCV-coinfected patients in comparison with HCV monoinfected, the HIV-, HCV-, and host-/genetic-related factors, as well as the exact mechanisms implicated in this process, are not fully elucidated. Furthermore, cure of HCV in those coinfected seems possible with the new antiviral drugs, but high cost as well as insufficient identification, linkage with care, and treatment hamper the achievement of this goal. Research on the individual could reveal an important prognostic marker for the effectiveness of persuasion of patients with HIV/HCV coinfection with a predicted accelerated fibrosis course, to facilitate and prioritize, not only in terms of guidelines but also in the real-life situation, their treatment with a medically just framework. **(AIDS Rev. 2017;19:148-155)**

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Key words

HIV. Hepatitis C virus. Coinfection. Liver fibrosis.

Introduction

It is known that after the introduction of combination antiretroviral therapy (cART) the overall morbidity and mortality of HIV-infected patients reduced dramatically. As HIV individuals live longer, other comorbidities are affecting their clinical course. Liver-related complications are increasingly prevalent in patients living with HIV/AIDS accounting for 9% of deaths in unselected HIV-positive patients. Causes of liver disease include viral hepatitis, non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis, drug-associated toxicities, and metabolic/genetic disorders[1].

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HIV and hepatitis C virus (HCV) coinfection are quite common due to the fact that they are transmitted through the same route (parenteral, sexual, and vertical). In a recent meta-analysis, Plat et al. estimated that worldwide there are approximately 2,278,400 HIV-HCV-coinfected individuals, equaling an overall coinfection prevalence of 6.2%[2]. HCV prevalence was consistently higher in HIV-positive compared with HIV-negative in all risk groups that were studied, but especially in people who inject drugs (82.4%).

The exact impact and immunologic effect of HIV in HCV infection are not completely understood[3]. Many studies, but not all of them, concluded that coinfected individuals experience an accelerated liver fibrosis process. The consequent rise in the incidence of liver complications outlined the need for better understanding of the involved mechanisms.

Furthermore, the response to classical HCV therapy was poorer in coinfected patients. The development of the new direct-acting antivirals (DAAs) against HCV seemed very promising for the eradication of HCV in both HIV and non-HIV patients with further benefits of the reduction of the complications and transmission rates. Despite the high rates of efficacy proved equal for both HCV and HCV/HIV[4-6], only a small number of the HCV/HIV patients are actually treated with these new therapies because of their cost. Although the AASLD[7] and EASL[8] now recommend that individuals coinfected with HIV are prioritized for treatment regardless of their fibrosis stage, there is heated debate as to how best prioritize patients for treatment because reimbursement of HCV therapy is often restricted in many countries to individuals with advanced liver fibrosis. Even cost-effective treatments will need to be rationed to manage the health budget[9].

Beyond the cost, another factor complicating the treatment of coinfected individuals is that the cascade of care is far from perfect even in developed countries. The Centers for Disease Control estimates according to the Annual National HIV/AIDS progress report that while 87% of people living with HIV know their serological status, only 72.6% are linked to care within 1 month of diagnosis, 56.5% are retained in HIV medical care, and from those on cART, only 54.7% of them have efficient suppression of the virus[10]. The implications of this observation with regard to HCV coinfection are evident since specific groups of HIV-infected like those who inject intravenous drugs and patients with severe psychiatric disorders are less likely to access care for HIV and less likely to be treated for HCV.

The aim of this review is to describe the mechanisms implicated in liver fibrosis in HIV-/HCV-coinfected individuals that might form the basis for a better approach to identify and treat these patients.

Liver Fibrosis in HIV-HCV Coinfection

Reports have demonstrated a more accelerated liver fibrosis progression in the setting of HIV-HCV coinfection and liver disease as a major cause of morbidity and mortality in the coinfected population. The widespread introduction of modern, effective, and less toxic cART regimens altered some of the observations. Two types of HIV-/HCV-coinfected patients have been reported, those infected for many years and treated with older antiretrovirals in the past and those recently infected who are treated with the newer ART.

Several studies report higher progression rates in coinfected compared to monoinfected patients while others have shown similar rates. Higher prevalence of advanced fibrosis in the coinfected as compared with HCV-monoinfected population was the result reported by Avihingsanon et al.,[11] Brescini et al.,[12] Li Vecchi et al.,[13] Sagnelli et al.,[14] Ragni et al.,[15] Martin-Carbonero et al.,[16] Castera et al.,[17] Gaslightwala and Bini,[18] and Gonzalez et al.[19] On the contrary, Mazzocato et al.,[20] Tovo et al.,[21] Suárez-Zarracina et al.,[22] Sterling et al.,[23] Grunhage et al.,[24] and Souza et al.[25] report similar progression rates. There are methodological issues with most of these studies. Some of them were longitudinal, others were cross-sectional, the fibrosis assessment method was not the same, and finally, other important factors such as alcohol use, smoking, gender, and duration of HIV infection were unequally distributed between HIV/HCV and HCV cohorts[26]. These aspects may in part explain the conflicting reports regarding the fibrosis process in the liver of coinfected patients.

Several factors might influence liver fibrosis progression rate and can be related with HIV, HCV, and the host. In coinfected individuals, worth considering parameters are as follows: (1) HIV viremia; (2) changes in the degree of immune suppression (i.e., CD4 cell count); (3) the duration and extent of significant HIV-induced immune activation in part maintained by microbial translocation from the gut; and (4) the hepatotoxic potential of antiretrovirals. Of course, this is irrespective of the roles of steatosis, alcohol, insulin resistance (IR), and hepatitis B virus (HBV) coinfection in fibrosis progression, which is important in both HIV-/HCV-coinfected and HCV-monoinfected patients.

However, it must be noted that these factors are more common among people living with HIV comparing with HIV-negative people.

HIV viremia

HIV viremia seems to be of great importance in the liver fibrosis process. In a substudy of the INSIGHT Strategic Timing of Antiretroviral Treatment trial HIV, RNA levels were associated with higher fibrosis score at baseline (before the initiation of cART) among the 230 participants who were enrolled in this substudy[27].

The introduction of the new cART has led to the better control of HIV viremia. However, there is evidence of residual viral replication, especially in specific sanctuary third space body compartments. This phenomenon is present even in cases of an effective therapeutic outcome. The subsequent result is the chronic non-specific activation of the immune system. This phenomenon of systemic inflammation has also been associated with a more rapid fibrosis progression.

HIV can cause the activation of the chemokine (C-C motif) receptor 5 (CCR5) and cysteine-X-cysteine receptor 4 (CXCR4) coreceptors of the hepatocytes[28-31], the hepatic stellate cells (HSCs)[32], Kupffer cells, HIV-specific T-cells, and interleukin-17 (IL-17) producing T-cells, thus resulting in a chronic non-specific activation of the immune system[33]. This particular systemic inflammation process has also been associated with a more rapid liver fibrosis progression.

Bacterial translocation

Bacterial translocation has an important impact on liver fibrosis in HIV-/HCV-coinfected patients[34]. The loss of integrity of gut mucosa is the result of the HIV viral action on the intestinal wall, especially on the CD4 T-lymphocytes and macrophages. The subsequent increased microbial translocation results in activation of the Kupffer cells and HSCs through various mediators, consequently promoting liver fibrosis[35,36].

Immune suppression

Immune suppression is more profound in HIV infection and is mainly expressed with the reduction of the CD4 cells. Data from the previous studies correlated the low CD4 counts with the progression of fibrosis[37]. The most recent guidelines of the EACS, DHHS, and WHO recommend the initiation of highly active antiretroviral therapy early and irrespective of the CD4 count. However, an important percentage of people living with HIV/AIDS is not still on cART, and many of those on therapy cannot restore the CD4 count in levels similar to non-HIV individuals[38].

Antiretrovirals

The crucial factor that differentiates HIV/HCV from HCV-monoinfected patients is the antiretroviral drugs. cART has changed not only the natural history of HIV infection improving dramatically life expectancy but also the quality of life. Nevertheless, side effects derived from the use of these agents were recognized. It is well-known that some of the antiretrovirals affect the liver. The older nucleoside reverse-transcriptase inhibitors (NRTIs), didanosine, and stavudine (d4T) have been associated with the development of liver fibrosis and portal hypertension[22,39]. NRTI also can cause mitochondrial toxicity which predisposes to liver injury and subsequent fibrosis. Protease inhibitors, another large category of antiretrovirals, can also worsen the deposition of fat in the liver and consequently liver fibrosis. First, they can decrease peripheral lipolysis through inhibition of glucose transporter Type-4 activity. The adipocytes in the peripheral tissue and abdomen become hypertrophic, lose part of their activity, and consequently become resistant to insulin. These adipocytes secrete less adiponectin, resulting in an increase of body fat and worsening the deposition of fat in the liver and tissue fibrosis[40].

Non-NRTIs are known for their potential to cause elevated liver enzymes but have so far not been linked to fibrosis progression and are the drugs most commonly utilized. However, prospective data are needed to be able firmly to conclude about their hepatic safety.

HIV-/HCV-coinfected patients diagnosed in more recent years who started therapy earlier with the newer more effective and safer antiretroviral drugs are distinctly different from those who have been exposed to longer duration of unsuppressed HIV and hepatotoxic drugs. Current evidence suggests that the first group may exhibit a much more similar liver fibrosis progression rate as HCV-monoinfected patients[26].

Genetics of Liver Fibrosis in HIV-/HCV-coinfected Patients

A number of candidate genes have been used to identify variants influencing the development of liver disease in patients with HCV infection, but the vast

majority of them produced results that were not consistently replicated. Genome-wide association studies (GWAS) provide a broader, unbiased approach for the discovery of genetic factors involved in disease susceptibility. In HIV-related phenotypes, such studies have mostly identified HLA loci associated with the control of viral load and with nonprogression to AIDS. Several GWASs of HCV infection-related phenotypes have identified polymorphisms of the IL28B (also denoted as IFNL3/4) gene associated with the spontaneous clearance of HCV and a favorable response to interferon-/ribavirin-based treatment, both in patients infected with HCV only and in patients with HIV/HCV coinfection. By a candidate gene approach, polymorphisms of IL28B gene have also been associated with liver inflammation and hepatic fibrosis in HCV monoinfection. Only two GWASs have focused on the HCV-related liver fibrosis outcome in patients with monoinfections[48,49].

The identification of genetic variants associated with a risk of developing liver fibrosis in this specific population of coinfected patients is therefore of major interest.

A recent GWAS[50] detected, for the first time, two significant signals associated with severe liver fibrosis in patients with HIV/HCV coinfection. One of these signals was weaker if patients with sustained viral response (SVR) were removed from the analysis and was not replicated in two cohorts of patients with HCV monoinfection. By contrast, the signal on chromosome 3p25 clearly remained significant in the sample of coinfected patients without SVR and was replicated in two independent cohorts of patients with HCV monoinfection, through the highly correlated SNPs rs61183828 and rs73132859. The biologic role of two genes, *CAV3* and *RAD18,* appear interesting as their products are involved in mechanisms likely to affect both cell signaling and the maintenance of cell structure for *CAV3* or implicated in the post-replication DNA repair process occurring during HIV-1 infection and maximize HCV replication for *RAD18*.

In this GWAS, a significant replicated genetic association on chromosome 3p25 with the SNP rs61183828 was identified, which exhibits a substantial impact on liver stiffness in coinfected patients. These results suggest new relevant hypotheses for the pathogenesis of liver fibrosis in coinfected patients, pointing out novel molecular mechanisms potentially accounting for this genetic effect.

Other factors

In addition to these HIV-related factors, the role of steatosis, IR, and alcohol consumption are all important in both HIV-/HCV-coinfected and HCV-monoinfected patients. However, the incidence and importance of some of these factors are higher among people living with HIV/HCV.

The incidence of NAFLD in HIV-positive population is about 30–40%, higher than the estimated incidence in HIV-negative persons. Furthermore, there are data supporting that fatty infiltration of the liver occurs in patients with lower body mass index values as compared to HIV-negative people, suggesting a possible lower threshold for this complication. Similarly, steatohepatitis is more common in HIV-infected patients[41-43].

IR is a known factor that promotes liver fibrosis[44]. The incidence of IR, in many studies that tried to calculate it, is higher among HIV-positive patients[45].

Finally, alcohol and cannabis consumption is higher among some groups of people living with HIV/AIDS, facilitating as cofactors the fibrotic process[46,47]. This is another cofactor of liver disease in HIV-/HCV-coinfected patients that can contribute to a worst fibrosis progression compared to the HCV-monoinfected persons.

Pathogenesis/Immunobiology of Liver Fibrosis in HIV-/HCV-coinfected Patients

At the liver molecular level, HIV infects or signals multiple types of intrahepatic cells, documented both *in vitro* (cell lines and primary cells, hepatocytes, Kupffer, stellate, and endothelial cells) and *in vivo* (hepatocytes and Kupffer cells).

HIV entry to hepatocytes is through the cell-surface coreceptors CCR5 and CXCR4. Their activation increases the expression of procollagen alpha-1, a component of Type 1 collagen. The latter can be detected in the extracellular matrix (ECM) that is characteristic of advanced fibrosis[28,29]. Furthermore, HIV can directly induce death of the hepatocytes, mostly by increasing cell susceptibility to the TNF-related apoptosis-inducing ligand receptor (TRAIL)[30,31]. HCV hepatocyte apoptotic bodies, engulfed by stellate cells, lead to their activation with subsequent increase fibrosis[51].

HIV isolates can infect primary human HSCs, and HIV causes a productive noncytopathic infection of Kupffer cells (lipopolysaccharide hyperresponse). Furthermore, HIV increases stellate cell activation, either as a result of direct HSC activation by damage-associated molecular patterns (DAMPs) or indirect DAMP-induced Kupffer cell activation with subsequent IL-1β- and IL-18-mediated HSC activation.

The result of direct effect is the subsequent expression of monocyte chemoattractant protein-1 (MCP-1) and activation of tissue inhibitor metalloproteinase (TIMP). Both proteins act as chemoattractants of leukocytes, thus promoting liver inflammation and fibrosis[32]. Furthermore, CCR5, CXCR4, and glycoprotein 120 mediate stellate cell activation[33]. CCR5 and CCL5 mediate HSC migration and proliferation, as well as "cross-talk" between HSCs and leukocytes during fibrogenesis.

Disruption of CCR2 and CCR5 signaling pathways is expected to provide anti-inflammatory and antifibrotic benefits. Cenicriviroc (CVC), an antagonist of the CCR2 and CCR5 receptors and their respective ligands, C-C chemokine ligand Type 2 (CCL2/MCP-1) and 5 (CCL5/RANTES), is expected to have the aforementioned activities[52].

The mechanisms by which CVC may prevent inflammation and fibrosis in HIV-/HCV-coinfection are decreased recruitment, migration, and infiltration of pro-inflammatory monocytes to the site of liver injury induced by activated Kupffer cells, mainly through CCR2 antagonism. This consequently reduces the number of pro-inflammatory macrophages in the liver, thereby decreasing chronic liver inflammation and downregulating the production of profibrotic cytokines, such as transforming growth factor beta-1 (TGF-β1) that promotes the transdifferentiation of HSCs to collagen synthesizing myofibroblasts.

Chronic liver injury induces fibrosis that is characterized by the accumulation of ECM proteins and is modulated by cytokines regulating the inflammatory response[47,53-55]. Among many cytokines and growth factors, TGF-β/activin superfamily along with the major downstream mediator of its signaling, namely, connective tissue growth factor play a pivotal role in hepatic fibrogenesis and development of cirrhosis. TGF-β1 promotes the transdifferentiation of HSCs to collagen synthesizing myofibroblasts and the production of tissue inhibitors of metalloproteinases, which inhibit the metalloproteinase-mediated degradation of ECM components.

Blockade of TGF-β signaling in animal models inhibits the fibrotic response in the liver, whereas transcriptional activation of TGF-β induces plasminogen activator inhibitor-1 and ECM proteins production[56,57].

TGF-βs and activins transduce their signals by binding to specific transmembrane receptors and activating their intracellular mediators, namely, the receptor-regulated SMAD (mothers against decapentaplegic drosophila homolog) proteins (R-SMADs), especially SMAD2 and/or SMAD3. After their activation, R-SMADs associate with the common-mediator SMAD (co-SMAD), namely, SMAD4 resulting in the translocation of the SMAD complex into the nucleus to regulate the expression of target genes. Hepatitis viruses can also affect the TGF-β signaling through interaction with both receptors and SMADs. The dominant intracellular antagonist (and regulator) of TGF-β/activin signaling is SMAD family member 7 that acts to attenuate the TGF-β-mediated fibrosis in multiple organs, including the liver[58].

In an *in vitro* model of coculture of hepatocyte and HSC lines Huh7.5.1 and LX2, both HCV and HIV independently activated TGF-β1 signaling through reactive oxygen species (ROS) (antioxidant response elements), nuclear factor kappa-light-chain-enhancer of activated B-cells (NFκB), and SMAD3 in both cell lines in coculture. Activation of these profibrotic pathways was additive following HIV/HCV coexposure. This was confirmed when examining collagen

Type 1 alpha-1 and TIMP1, where messenger RNA and protein levels were significantly higher in LX2 cells in coculture following HIV/HCV coexposure, compared with either virus alone. In addition, expression of these profibrotic genes was significantly higher in the coculture model compared to either cell type in monoculture, suggesting an interaction and feedback mechanism between Huh7.5.1 and LX2 cells. HIV in these experiments seems to accentuate an HCV-driven profibrogenic program in hepatocyte and HSC lines through ROS, NFκB, and TGF-β1 upregulation[59].

An important pathway of inflammation associated with viral infection is activation of inflammasomes[60]. Inflammasomes are molecular platforms activated on cellular infection or stress that triggers the maturation of pro-inflammatory cytokines such as IL-1β to engage innate immune defenses. The NLRP3 (NACHT, LRR, and PYD domains-containing protein 3/cryoporin), inflammasome is a cytosolic protein complex required for the development of sterile inflammation that can further increase organ damage. Many liver diseases such as alcoholic steatohepatitis, nonalcoholic steatohepatitis (NASH), and drug-induced liver injury have sterile inflammation as a major component.

In viral infections, pathogen sensing promotes the assembly of these molecular platforms. The result is the secretion of the pro-inflammatory cytokines IL-1β and IL-18 known to mediate inflammation[60]. Studies have shown that viremic HIV-infected individuals have higher plasma levels of IL-18 compared to uninfected and ART-treated individuals[61,62]. In a recent study, Veenhuis et al.[63] showed that IL-18 is higher in coin-

fected than in monoinfected or uninfected individuals. Interestingly, comparing HIV- or HCV-monoinfected patients, IL-18 levels were significantly higher in those with HIV infection suggesting a more potent induction of the inflammasome activation by HIV. There is also, however, a marked person-to-person variation in the inflammasome response to HCV and HIV. 11 highly correlated single-nucleotide polymorphisms ($r^2 = 0.98$-1) in the IL-18-BCO2 region were found significantly associated with IL-18 levels in serum. Thus, genetic variation in IL-18 is associated with IL-18 production in response to HIV and HCV infection and may explain variability in the inflammatory outcomes of chronic viral infections[64].

Given the association between IL-18 and the inflammatory complications, increased inflammasome activation and consequent IL-18 secretion may explain enhanced liver disease progression observed in coinfected individuals.

Among the most powerful mechanisms for achieving a balanced immune response are the expression of programed death 1 (PD1) molecule by T-cells and the inhibition of effector T-cells (Teffs) by CD4+-T regulatory cells (Tregs)[65-68]. Models of viral infection have indicated that the interaction between the inhibitory receptor PD1, expressed in high levels on lymphocytes, and its ligands program cell death 1 ligand (PDL1) and PDL2, plays a critical role in T-cell exhaustion by inducing T-cell inactivation[65,69]. The previous studies have indicated that patients with chronic viral hepatitis display increased numbers of Tregs (both natural and inducible) in peripheral blood or liver, which, in turn, exert a suppressive function against specific HCV-Teffs *in vitro*[70].

Recently, Speletas et al. demonstrated that the *FOXP3* expression in liver is positively correlated with the intensity of liver inflammation along with a specific pattern of mRNA expression of the apoptosis mediators *FAS*, *FASL*, and *TRAIL*, irrespective of the cause of tissue damage (viral, toxic, and autoimmunity) suggesting that might represent a bystander effect and not a causative event of chronic inflammation[71].

NAFLD is clearly, in this era of safer and more effective hepatitis C therapy, common in patients with HIV and might be more likely to progress to NASH- and NAFLD-related fibrosis or cirrhosis in these patients than in individuals without HIV. Very little is known about the pathogenesis of NAFLD in patients with HIV and the extent to which HIV, ART, and metabolic syndrome account for its increased prevalence. As in patients without HIV, the accumulation of excess fatty acids in the liver and the progression to hepatocyte injury, inflammation, and fibrosis in patients with HIV are a part of a complex process that has no single pathophysiological mechanism. We need to emphasize that many of the above-analyzed concepts on accelerated fibrosis progression in the liver of people living with HIV may be important to understand and manage NAFLD/NASH in HIV[72].

Conclusions

The reduction of HIV-related morbidity and mortality after the introduction of cART revealed the increasing incidence of the liver-related complications among people living with HIV. This fact led the medical community of HIV medicine to focus on the pathogenesis and treatment of the liver disease in these patients. HIV/HCV coinfection is an important etiological factor of liver complications.

Previously conducted studies tried to determine whether liver fibrosis progress is more rapid in HIV/HCV coinfected as compared to HCV-infected individuals with conflicting results.

However, several factors possibly affect this process. Factors associated with HIV infection such as HIV viremia, reduction of CD4 lymphocytes, bacterial translocation, and toxicity of some of the antiretrovirals seem to be implicated. They may act in synergy with traditional factors such as alcohol and drug abuse, NAFLD, and IR which are more frequently present among HIV-/HCV-coinfected than in HCV-monoinfected patients. All these factors influence the fibrosis progression, promoting the development of liver complications.

The arrival of the new DAAs offers the possibility of eradication of hepatitis C in HCV/HIV coinfection. HCV cure rates in coinfected patients treated with DAAs are equivalent to those seen in the HCV-monoinfected patients because the new DAAs act on virus replication without the mediation and need of specific immune responses. A major barrier to this target is the cost of the DAAs. Further study and understanding of the pathogenesis of liver disease in HIV-/HCV-coinfected patients will help in prioritizing the HCV therapy. New research findings on the mechanisms of accelerated liver fibrosis in HIV-HCV coinfection will probably support current recommendations to start HCV treatment irrespective of fibrosis stage in those with risk factors for accelerated fibrosis progression and persons at elevated risk of HCV transmission.

These results will possibly suggest new relevant hypotheses for the pathogenesis of liver fibrosis in

coinfected patients, pointing to novel molecular mechanisms potentially accounting for this effect. These findings may help to define new targets for the development of drugs or prognostic tools in the treatment of HCV-infected patients.

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