Chapter 3

Immune Disorders in HIV-Infected Patients Coinfected with Hepatitis C Virus

Konstantin Shmagel and Evgeniya Saidakova

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Abstract

In Russia, more than half of HIV-infected people are coinfected with hepatitis C. Both viruses interact with the immune system compounding the disease course. HIV infection accelerates the onset of hepatitis-mediated liver fibrosis and cirrhosis. Hepatitis C slows down the recovery of CD4+ T-lymphocytes during antiretroviral treatment and fuels the already intense chronic inflammation. In the present review, we discuss coinfection prevalence and reasons for its abundance, provide extensive coverage of the known mechanisms that give rise to the detrimental health effects in HIV/hepatitis C-coinfected patients, and report our own data on the double infection consequences in people with discordant immunologic response to treatment.

Keywords: HIV infection, hepatitis C, HIV/HCV coinfection, innate immunity, adaptive immunity, discordant immunologic response, highly active antiretroviral therapy

1. Introduction

More than any other infectious disease, HIV infection claims to be called "the coinfection illness" [1]. Coinfections can significantly change the illness pattern and the immune activation profile [2–4] and typically lead to the rise in morbidity and mortality [5–7]. The coinfection most often associated with HIV is hepatitis C virus (HCV) infection. This is due to the worldwide prevalence of both illnesses (there are approximately 40 million HIV-infected and about 120 million HCV-infected subjects worldwide) and the overlap in infection transmission routes [8, 9]. In Western Europe and the United States, the proportion of hepatitis C chronically infected patients among HIV-positive people is 25–30% [10], and in Eastern Europe, it is more than 50% [11]. In Russia, the increase in injection drug use has led to a significant rise

in the prevalence of HIV/HCV coinfection. Its level among drug users reaches 93% [12]. The problem is complicated by the rise in non-AIDS-defining morbidity and mortality in HIV/HCV-coinfected subjects [13, 14].

There is considerable evidence that HIV infection adversely affects the course of a hepatitis C infection. When HIV/HCV coinfection is compared with HCV monoinfection, a more rapid fibrosis [15, 16] and liver cirrhosis [16, 17] are observed. Coinfected subjects also have an increased risk of hepatocellular carcinoma, which occurs at an earlier age and in a shorter time interval after HCV infection [18–20]. It was found that HIV/HCV-coinfected patients compared to HCV-monoinfected patients were more resistant to interferon therapy. In HIV-seronegative subjects infected with HCV genotype 1, 50–80% can achieve a complete recovery. However, in HIV-seropositive individuals coinfected with the same HCV type, interferon therapy is successful only in 20–35% of patients [21]. This accounts for the increased mortality rate among HIV-/HCV-coinfected patients when compared with HIV-monoinfected patients [22, 23].

Less is known about the effect of hepatitis C on the natural course of HIV infection. Among the negative influences, one can point to direct viral effects, hepatocyte destruction by immunocompetent cells, hepatic cell apoptosis, immune activation, and specific antiviral immune response alterations [24–26]. The complexity of the problem is largely due to the lack of knowledge about the biology of both HIV and HCV. It remains unknown whether the viruses interact with each other and in what ways that interaction might be expressed.

2. Liver fibrosis in HIV/HCV coinfection

Evidence indicates that the HCV viral load is lower in hepatitis C-monoinfected patients when compared to HIV/HCV-coinfected patients [27, 28]. Similar results were obtained when estimating the viral load in hepatic tissue [29]. In addition, multiyear cohort studies state that in patients with hepatitis C the HCV RNA blood level significantly increases after exposure to HIV [30, 31]. HCV replication enhancement in coinfection is attributed to both the development of immunodeficiency and the direct impact of HIV. While attempting to determine the mechanism(s) of these effects, it was shown that inactivated HIV or its component (gp120) can intensify viral replication in HCV-infected hepatoma cells in vitro [32]. This effect of HIV was shown to be due to transforming growth factor-beta 1 (TGF-β1) synthesis (antibodies against the cytokine blocked the HCV replication enhancement). Researchers also noted that HIV engages CCR5 or CXCR4 co-receptors for the related intracellular signal induction. Those data are significant not only for demonstrating the ability of HIV to increase HCV replication (with a monoinfection of hepatitis C, viral load is usually not associated with the disease severity) but also for illuminating the possible pathogenetic mechanism of fibrosis in HIV/HCV coinfection.

In many studies, HIV/HCV-coinfected patients demonstrated an inverse correlation between the CD4+ T-cell count and the HCV viral load [33–37]. Moreover, in those patients, low CD4+ T-lymphocyte quantity was used as a liver fibrosis predictor [34, 38, 39]. This suggests a negative impact of HIV infection on the course of hepatitis C through the development of CD4+ T-cell deficiency. It should be noted that a decrease in the CD4+ T-lymphocyte count is also found in those monoinfected with HCV. Indeed, the majority of HIV-seronegative subjects

with liver cirrhosis have a reduced CD4+ T-cell count [40, 41]. Most researchers state that HIV infection, accompanied by a profound depletion in the CD4+ T-lymphocyte pool, is a prominent mediator of the accelerated liver fibrosis development in HIV-/HCV-coinfected people [42–44]. Based on those results and the opinions of leading specialists, the European AIDS Clinical Society recommends the early administration of highly active antiretroviral therapy (ART) to HCV-coinfected patients not only to optimize their hepatitis C management but also to slow down the development of fibrosis [45].

The main cellular element involved in the process of hepatic tissue fibrosis is the liver stellate cell (LSC) [46–49] located around the sinuses and usually not showing high activity until the organ is damaged [50, 51]. However, various destructive processes in the liver are accompanied by the reaction of hepatocytes, endotheliocytes, and Kupffer cells to produce various humoral factors [52]. Of those, TGF-β1 [53, 54] and PDGF (platelet-derived growth factor) have the most pronounced effect on LSC [52, 55]. Both cytokines induce LSC activation and differentiation into myofibroblast-like cells, which actively synthesize extracellular matrix proteins [56]. However, it should be noted that TGF-β1 and PDGF blood concentrations (as opposed to analyzing the hyaluronic acid or hepatocytes' growth factor content) have no high diagnostic value for the detection of fibrosis [57–60]. Moreover, it has recently been established that HIV influences the liver by infecting hepatocytes and liver stellate cells [61].

3. Anti-HCV immunity in HIV/HCV coinfection

Protection against HCV is implemented by various factors with an important role for interferons, natural killer (NK) cells, neutralizing antibodies, and T-lymphocytes. Type I interferons (IFN-α and IFN-β) and type III interferon (IFN-λ) are synthesized in response to the virus and induce interferon-stimulated gene (ISG) expression [62, 63]. In the cytosol, the pathogen's RNA is detected by the RIG-I (retinoic acid-inducible gene I) sensors, protein kinase R, and MDA5 (melanoma differentiation-associated protein 5). The first two mediate the interferon response at the early stages of the disease, and the third one mediates at the later infection phase [64, 65]. In endosomes, the virus is primarily detected by Toll-like receptor 3 (TLR3) that also triggers the IFN production and the ISG expression [66]. In hepatocytes of HCV-infected patients, the viral RNA and ISGs' mRNA are detected simultaneously, which confirms the connection between the cell genetic response and the presence of the pathogen [67]. The result of the activated ISG status in HCV infection leads to viral replication inhibition [68, 69]. However, prolonged ISG expression has a negative effect on the process of HCV spontaneous elimination [70, 71] and on the results of interferon and ribavirin combination therapy [72, 73].

NK cells play an important role in the pathogenesis of an HCV infection. It was found that in the healthy liver they represent the majority of the innate immune cells [74]. In the acute phase of the disease, NK cells affected by the virus are activated, produce IFN-γ, and perform cytotoxic functions [75]. In the chronic infection phase, IFN-γ and tumor necrosis factor (TNF)-α synthesis are reduced [76–78] even though the NK cell cytotoxic potential remains high [79, 80]. Since the protective effect of IFN-γ was demonstrated in HCV-infected hepatoma cells [81] and in experiments with chimpanzees given primary and repeated infections [82], it is

believed that reduced IFN-γ production weakens the NK cell's antiviral activity. Thus, in the chronic stage of HCV infection, in spite of being activated and ready to perform cytotoxic functions, the NK lymphocytes are unable to effectively resist HCV due to the failure of IFN-γ production. However, the saved killing function can produce a positive result. NK cells from HCV-infected subjects are capable of killing activated LSC by NKG2D- and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-dependent apoptosis, which allows them to be considered as active participants in liver fibrosis suppression [83].

The role of neutralizing antibodies (nAB) in protection against an HCV infection is not yet sufficiently understood. Based on known cases of spontaneous recovery before nAB emerge [84] and based on the ability of some patients with hypogammaglobulinemia to control the infection [85, 86], it could be concluded that the humoral immune response does not determine resistance to the disease. At the same time, there is evidence of a protective function for antibodies directed against HCV surface proteins. HCV envelope glycoprotein E1 and glycoprotein E2 seroconversion is usually observed a few weeks after an infection [87]. The ability of viral envelope-specific antibodies to block the infectious process was demonstrated in chimpanzees [88, 89] and in mice with genetically humanized liver [90, 91]. The emergence of nAB in the acute phase of HCV infection is accompanied by an alteration in the virus and its escape from immune control [92]. The authors also showed that despite the increased virus flexibility, high antibody titers significantly increase the chance for clearance of the infection. The acute-phase nAB titers are usually low in patients subsequently entering the chronic stage of the disease.

As was established in monkeys with induced CD4+ or CD8+ T-cell deficiency [93, 94], T-lymphocytes play an important role in the development of hepatitis C. It should be noted that the HCV-specific T-cell response usually develops 2–3 months after the infection [95, 96], although according to some authors such a "slow" reaction has little effect on the disease outcome [84]. It seems that the quality of the immune response achieved by CD4+ and CD8+ T-cells is a more important factor [97, 98]. It was found that in the acute phase of the infection, patients spontaneously clearing HCV compared to subjects in whom the disease became chronic had a more robust CD4+ T-lymphocyte response, which manifested in more active proliferation and cytokine (IFN-γ, TNF-α, and IL-2) production [99–102]. Later, it was found that the expression of PD-1 (programmed cell death protein 1) and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) inhibitory molecules was increased on the surface of CD4+ T-cells in patients chronically infected with HCV [103]. Blocking of PD-1 ligand (PD-L1/PD-L2), IL-10, and TGF-β1 in cultured lymphocytes isolated from the blood of these patients increased the virus-specific expansion of CD4+ T-lymphocytes. Neutralization of IL-10 and TGF-β1 enhanced the synthesis of IFN-γ, IL-2, and TNF-α. Further studies revealed that IL-21-producing CD4+ T-lymphocytes are lost in individuals with a chronic hepatitis C infection [104]. It has also been demonstrated that the deficiency of Th17 cells synthesizing IL-21 limits the HCV-specific CD8+ T-lymphocyte function and survival. The inability of CD4+ and CD8+ T-cells to control viral replication leads to their exhaustion. According to the authors, in chronic HCV infection, the increase in regulatory T-cell number and activity is aimed at suppressing an ineffective immune response and reducing inflammation. The other side of that process is fibrosis intensification. Thus, based on the above data, one can conclude that CD4+ T-lymphocytes are the key cells in protection against HCV. Hence, it becomes clear why a low CD4+ T-cell count is a negative predictor for liver fibrosis development in HIV-/HCV-coinfected patients.

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4. Detrimental effects of hepatitis C on the course of HIV infection

It is more difficult to assess the effect of hepatitis C on the natural course of HIV infection. One of the parameters characterizing that effect is CD4+ T-cell count reconstitution after the administration of ART. To date, the accumulated data indicate slowing of the CD4+ T-lymphocyte restoration process in HIV-positive subjects coinfected with hepatitis C [35, 105–108]. The rate of CD4+ T-cell counts increases after receiving ART was reduced sevenfold in coinfected individuals compared with HIV-monoinfected patients [35]. The authors also established an association between impaired immunity regeneration and the level of HCV replication. In another study, it was demonstrated that in hepatitis C-positive patients, ineffective ART-mediated restoration affected not only the total CD4+ T-lymphocyte numbers but also their naive subset [106]. However, it should be noted that not all researchers support the idea of the negative effect of HCV coinfection on the treatment-induced CD4+ T-cell response [109, 110]. Still, an extensive multicenter study involving 22,533 patients showed that immune regeneration during ART is slower in coinfected patients, and the lower the nadir CD4+ T-lymphocyte level, the more pronounced the effect [111]. However, as noted in the paper, the differences in the CD4+ T-cell recovery between HIV + HCV+ and HIV + HCV− subjects are canceled by early treatment administration and uninterrupted long-term ART.

HIV infection causes severe devastation in the lymphoid structures of the digestive tract. It is accompanied by intestinal epithelial barrier destruction [112, 113] and the entry of microbes and their products into the bloodstream [114]. The increase in intestinal permeability is due to the direct destructive effect of HIV on the intestinal epithelium [115] followed by the development of inflammation and tissue remodeling [116]. Another cause for the pathological changes to the epithelial barrier is the deficiency of lymphocytes producing IL-17 and IL-22 which are necessary to maintain the epithelial lining integrity [117, 118]. To date, the role of microbial translocation in the immune system activation has been well established [119–121]. In addition, it has been shown that the blood levels of lipopolysaccharide (LPS) and soluble macrophage receptor CD14 (sCD14, capable of binding LPS) in HIV-infected patients can be used to predict disease progression and mortality [122–124]. Recently, in a large cohort of non-treated HIV-infected patients, an association between LPS-dependent immune activation and intestinal damage markers in serum was demonstrated [125]. However, a relationship between the immune system activation and viral load in blood was not found. Other data obtained in a study of bacterial-induced immune activation in patients with suppressed viral load also confirm its independence from the HIV load in blood [121, 126, 127]. It is assumed that the immune activation is mediated through TLRs [128–130].

It is widely accepted that liver cirrhosis compounds microbial translocation from the intestine into the bloodstream. A comparison of sCD14 blood levels in HIV/HCV-coinfected subjects, with varying degrees of liver fibrosis, showed that in patients with higher cirrhosis the soluble receptor concentration was more than in subjects with minimal organ destruction [131–133]. In HIV infection, the role of cirrhosis in the enhancement of the systemic inflammatory process was demonstrated while comparing two variants: compensated and uncompensated inflammations [134]. When uncompensated, a significantly higher level of LPS-binding protein (LBP) was detected in the patients' blood. The increase in the LBP content was accompanied by the rise in sCD14, sTNFR-I, and IL-6 concentrations.

Entry of large amounts of microbial products into the liver can have a negative impact on its function in HIV-infected individuals [135]. Liver cells actively express TLRs [136–139] that can interact with bacterial molecules and cause a marked inflammatory response in liver tissue [140, 141]. However, in experiments, it has been shown that prolonged exposure to LPS leads to a gradual decrease in the hepatocyte's sensitivity and a weakening of its ability to capture the bacterial lipopolysaccharide [142]. This causes a decrease in the detoxification function of the liver in patients monoinfected with HIV. The presence of hepatitis and cirrhosis additionally contributes to the decrease in LPS clearance by hepatocytes [143]. Consequently, in coinfection, microbial products entering the blood should cause strong immune activation. Indeed, the level of immune activation in HIV/HCV coinfection is higher than that in HIV [144, 145] or HCV [146, 147] monoinfection alone.

Activation of CD4+ and CD8+ T-cells is often followed by apoptosis: a phenomenon called "activation-induced cell death" (AICD) [148, 149]. AICD can be achieved through several mechanisms involving T-cell receptor stimulation, CD95, and various cytokines [150]. The role of innate immunity receptors in this phenomenon has also been established. Addition of various TLR ligands to cultured T-lymphocytes from healthy donors induced CD38 expression on CD4+ and CD8+ T-cells in short-term (less than 24 h) cultures [129]. Long-term culture (7 days) with TLR ligands led to a pronounced CD69 expression on CD8+ T-lymphocytes and Ki-67 expression in CD4+ T-cells. In such a case, CD8+ elements retained viability, and cycling CD4+ T-lymphocytes died. The data presented show how CD4+ T-cells, activated by microbial products, can die in HIV/HCV-coinfected patients. It is known that in untreated HIV-infected patients, HCV coinfection increases the apoptosis indices, but that effect is canceled by ART [151]. Later, the same authors found that in HIV/HCV coinfection, CD4+ T-lymphocytes are sensitized to Fas-induced apoptosis [152].

5. HIV/HCV-coinfected immunological nonresponders

A current concern is that as many as 30% of treated HIV-infected patients experience poor CD4+ T-cell restoration despite prolonged suppression of viral replication during ART (discordant immune response). These "immune nonresponders" (INRs) contrast with "immune responders" who recover their CD4+ T-cells to the normal range (>500/μL) while being treated. The discordant immune response is linked to an additional risk of mortality and non-AIDS-defining morbidities [153]. Still, the mechanisms responsible for insufficient CD4+ T-cell recovery during ART have not been fully discerned.

Our own studies have provided some additional information on the negative impact of hepatitis C on the natural course of an HIV infection. In our Russian cohort, we showed that HCV coinfection is a sufficient risk factor for the formation of a discordant CD4+ T-lymphocyte response to ART [154]. At the same time, we found that in coinfected patients when compared with patients monoinfected with HIV the increase in systemic inflammation was associated with liver damage and destruction of the hepatic barrier that protects against microbial products coming from the intestine [155]. INRs have a higher degree of hepatic tissue destruction and express more sclerosing processes [156]. We also found that HIV/HCV-coinfected

INR subjects are characterized not only by a deep CD4+ T-lymphocyte deficiency but also by decreased IL-2 production. Earlier, it was demonstrated [157] that through the secretion of this cytokine, T-cells can stimulate the natural killer cell's antifibrotic activity (realized through the killing of liver stellate cells). Thus, in HIV/HCV-coinfected INR patients, the IL-2 deficiency may be regarded as a liver fibrosis-accelerating factor.

In summary, it can be concluded that HIV/HCV-coinfected INRs are characterized by both a CD4+ T-lymphocyte deficiency and reduced IL-2 production which leads to liver destruction and cirrhosis formation. Under such conditions increased intestinal permeability (due to HIV infection) is supplemented by destruction of the hepatic barrier, accompanied by the entry of microbial products into the bloodstream. As a result, despite the ART-mediated HIV replication suppression, a pronounced systemic inflammation develops, leading to non-AIDS-defining diseases. Therefore, in coinfection, not only HIV infection therapy but also hepatitis C treatment should be actively carried out.

6. Conclusion

In HIV/HCV coinfection, the level of immune activation is higher than in HIV and HCV monoinfections. The transition of immunocompetent cells to the activated state is accompanied not only by their loss through the AICD mechanism but also leads to the development of non-AIDS-defining diseases, especially against the background of ART administration.

It can also be concluded that HIV infection exerts a greater influence on the natural course of a hepatitis C infection than the opposite. The key link in this influence is the depletion of CD4+ T-cells. However, not only CD4+ T-lymphocyte deficiency determines the HIV-negative impact on the development of hepatitis C. Even on the background of ART, HIV infection has a pronounced suppressive effect on NK cell activity against HCV. In HIV/HCV coinfection, a decrease in natural killer cell numbers and their ability to respond to IL-2 is observed. More importantly, the production of IFN-γ by those cells is also significantly impaired [158]. The outcome is the rapid development of liver fibrosis and cirrhosis.

As to changing the course of HIV infection against the background of hepatitis C, many questions remain. It is necessary to identify the main CD4+ and CD8+ T-cell subsets which are affected by HCV infection. In addition, studies of functional changes in T-lymphocytes like exhaustion [159–161], senescence [162–164], and loss of cytokine receptors [165, 166] must occur. It is also important to understand the nature of the immune system activation in HIV/HCV coinfection which is important in predicting the development of non-AIDS-defining diseases. Solving these issues requires further experimental and clinical research.

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Conflict of interest

The authors have no conflicts of interest to disclose.

Author details

Konstantin Shmagel[1,2]* and Evgeniya Saidakova[1,2]

*Address all correspondence to: shmagel@iegm.ru

1 Institute of Ecology and Genetics of Microorganisms, UB RAS, Perm, Russia

2 Perm State University, Perm, Russia

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