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Coinfection With HIV-1 and HCV—A One-Two Punch

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Abstract

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, cirrhosis, and death; it is estimated that 180 million persons are infected with HCV worldwide. The consequences of HCV are worse in those who are coinfected with human immunodeficiency virus 1 (HIV-1), which is unfortunately a common scenario because of shared risk factors of the viruses. More studies into effects of HCV/HIV-1 coinfection are needed, but efforts have been hampered by limitations in our understanding of the combined pathogenesis of the 2 viruses. Gaining insight into the mechanisms that underlie the immunopathogenesis of these persistent viral infections could lead to new therapeutic strategies for patients with HCV/HIV-1 coinfection.

The abilities of human immunodeficiency virus 1 (HIV-1) and HCV to establish persistent infections present unique challenges to the immune system. A shared characteristic of these infections is that they result in high-grade chronic viremia within the host that, unless treated, lasts indefinitely. The disease course is initially asymptomatic but then, over years to decades, results in destruction of the immune system (in the case of HIV-1 infection) or advancing liver fibrosis (in the case of HCV infection). Each virus causes considerable global health problems, and the two often meet in the same host because of shared risk factors for infection.

The effects of HIV-1 on the pathogenesis of HCV infection are deleterious and include a higher rate of viral persistence, increased viral loads, a faster rate of fibrosis progression, and higher rates of hepatic decompensation.[1] HIV-1/HCV–coinfected individuals have worse treatment outcomes following interferon (IFN)-based therapies compared with their HCV–mono-infected counterparts; moreover, liver transplantation is complicated for this population.[2] These clinical observations are accompanied by a suboptimal understanding of the pathogenesis of coinfection.

We review what is known about how these viruses interact with their respective host immune responses in coinfected individuals, with a dual focus on pathways to viral persistence and mechanisms that might underlie accelerated liver disease. In particular, we examine the potential role of the order of infection. Although the lack of a suitable animal model of coinfection has hindered studies of the mechanisms that underlie the interactions

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between the viruses and their immune responses, data from human and simian studies have yielded a variety of recent insights that could improve our understanding of the pathogenesis of persistent viral infections and the links between infection, inflammation, and fibrosis.

Pathways to Viral Persistence

After host entry, certain viruses have found ways to persist indefinitely. Some persist in a latent phase, with periods of reactivation and viremia (eg, herpes viruses). By contrast, HIV-1 and HCV have each evolved the ability to achieve an immensely high rate of replication (~10^9 particles/day for HIV-1 and ~10^{12} for HCV) that generally continues for years. The HIV-1 life cycle is fundamentally different from that of HCV; HIV-1 is a retrovirus that integrates into host DNA via the viral reverse transcriptase enzyme and the integrase complex, whereas HCV replicates via an RNA-dependent RNA polymerase and does not have a DNA intermediate. HIV-1 replication can be spontaneously controlled in a minority of individuals after infection, resulting in low or even undetectable plasma levels of virus and delayed progression to acquired immunodeficiency syndrome (AIDS) (Figure 1*A*). Understanding the mechanisms of spontaneous control and these so-called “elite controllers” of HIV-1 could contribute to the development of a prophylactic or therapeutic vaccine.[3]

After HCV infection, viremia occurs within days after infection with large inoculums of virus (eg, via a blood transfusion) or 6 – 8 weeks after the more common exposure to a smaller volume of virus (eg, that contained within a contaminated needle).[4] Ultimately, approximately 50%– 85% of infected individuals develop long-term persistent infections, characterized by a viral “set point” that generally does not vary by more than 10-fold (Figure 1*B*). A subset of hosts is able to clear the virus spontaneously. Viral clearance versus persistence is almost always determined during the first several months following infection, although cases of late spontaneous clearance have been documented.[5–7] Factors associated with clearance of HCV include female gender, younger age at acquisition, jaundice during acute disease, and nonblack race.[4]

The host immune system plays a role in the control of these 2 pathogens, evidenced by the mechanisms that each virus has evolved to establish persistent infection. A partial list of mechanisms for persistence of HIV-1 and simian immunodeficiency virus (SIV) is summarized in Table 1. While a detailed consideration of the immunopathogenesis of HIV-1 is beyond the present scope of this discussion, we refer the interested reader to several recent reviews.[3,8,9] As we turn to a more detailed discussion emphasizing the immunopathogenesis of HCV, we will highlight recent insights from studies on HIV-1 or SIV that are relevant.

Role of the Innate Immune System in Containing Viruses

Viral RNA is recognized by the innate immune system, initially via Toll-like receptors (TLRs) or the retinoic acid inducible gene I helicase. This initial interaction activates downstream signaling pathways that up-regulate the transcription factors IFN regulatory factor 3 and nuclear factor κB, leading to production of type I IFNs and induction of other antiviral effects that form the first line of defense against intracellular pathogens (reviewed in Gale and Foy[10] and Chung et al[11]). TLR7 agonism in particular has been pursued as a potential therapeutic intervention against HCV infection.[12] Interestingly, HCV proteins have been shown to interfere with these pathways, suggesting direct evasion mechanisms to circumvent the innate immune system.[13] Most intriguing is the observation that the HCV NS3/4 protease cleaves proteins that are required for innate immune signaling; this evasion strategy may be reversed by selective inhibitors of the HCV protease, such as telaprevir and boceprevir.[14–16] HIV-1 similarly engages these pathways, because it contains motifs within its nucleotide sequence that are recognized by TLR7 and TLR8.[17]

Innate effectors such as natural killer (NK) cells and natural killer T (NKT) cells also mediate antiviral defenses. For HCV, a genetic study showed that specific NK inhibitory receptor polymorphisms were associated with spontaneous clearance, but only in individuals with low initial inoculums (eg, injection drug users).[18] This study suggested that large inoculums, such as that received from a blood transfusion, can overwhelm these defenses. Furthermore, disruption of NK cell function could promote chronicity by alterations induced by chronic HIV-1 infection (such as increased activation and/or decreased cytokine secretion of NK cells induced by HIV-1)[19,20] or via direct interference by the HCV E2 protein,[21] although this latter result has not been verified in all in vitro systems.[22] NK and NKT cells constitute a significant proportion of liver-infiltrating lymphocytes during HCV infection,[23] promote virus-specific adaptive responses,[24] and in the case of NK cells can develop memory-like features.[25] A recent murine study in a liver fibrosis model demonstrated a role of NK cells in clearing senescent hepatic stellate cells,[26] which are activated by transforming growth factor (TGF)-β and are the primary profibrotic cell type within the liver.[27] More studies of NK and NKT cells and their relationship to dendritic cell function, the clearance of hepatic stellate cells, and the development and maintenance of T-cell function in the setting of HIV-1 are needed.

Role of the Adaptive Immune System in Containing Viruses

The next line of host defense is the adaptive immune system, which often controls or eradicates viruses but, in most cases, ultimately fails to contain HCV. With regard to humoral responses, antibodies capable of neutralizing HCV in vitro have been recognized[28]; however, their initial production in vivo is delayed compared with responses against other viruses. By the time successful neutralizing antibodies are produced, it is likely that the virus has mutated beyond recognition by this arm of the immune system.[29,30] Thus, HCV-infected individuals harbor antibodies that do not automatically provide immunity, as would be the case for antibody responses to other viruses, such as measles virus and varicella zoster virus. HCV reinfection of chimpanzees and humans is well documented, suggesting sterilizing immunity is rarely naturally acquired.[31,32] Nonetheless, as part of a preventive vaccine, induction of strong neutralizing antibodies that target conserved and immunogenic epitopes within the HCV envelope protein might achieve sterilizing immunity (abrogation of infection after exposure) if their presence is established before infection.[33]

There is growing consensus on the importance of T-cell responses in determining HCV clearance. First, genetic studies provide evidence for the importance of cell-mediated responses; polymorphisms in the HLA class I and class II molecules on chromosome 6, which determine the specificities of the CD8 and CD4 responses, respectively, are associated with spontaneous clearance.[34–37] Second, high-level T-cell responses (both virus-specific $CD4^+$ and $CD8^+$ cells in particular) have been detected during acute disease compared with chronic disease. These cells are responsible for identification and clearance of virus, either by cytolysis of virus-infected cells or noncytolytic clearance via cytokine or chemokine-mediated effects. Their appearance in the peripheral blood and at the site of infection is temporally associated with control of viremia; their disappearance is correlated with loss of control.[38–40] Third, longitudinal studies suggest the development of protective immunity, because those with evidence of spontaneous viral clearance are more likely to clear the virus upon reexposure[41,42]; depletion experiments in the chimpanzee model showed prolonged viremia if $CD4^+$ or $CD8^+$ T-cell memory responses were removed.[43,44] These types of immune responses could represent a prime goal for prophylactic vaccines that elicit protective immunity[45] and therapeutic vaccines (or immunotherapies) that reverse immune defects and boost immune function in infected individuals.[46] A parallel body of literature supports the role of T cells in control of HIV-1 or SIV infection, including genetic studies associating certain HLA alleles with spontaneous control,[3] studies of acutely

infected individuals,[47] and depletion experiments in simian models.[48] Ultimately, T-cell responses fail to control replication of either virus in the majority of cases.

These 2 viruses mutate to escape the adaptive immune response via their high replicative capacities and error-prone polymerases. Mutational adaptation to the T-cell response has been shown longitudinally within an individual in humans and in simian models of HCV and HIV-1 infection.[49–54] Changes in or around recognized viral epitopes lead to lack of intracellular processing, loss of peptide binding to the HLA, and/or reduction of binding affinity of the HLA-peptide complex to the T-cell receptor.[55] This phenomenon may be one of the major driving forces underlying the evolution of both HIV-1 and HCV (especially outside of the envelope proteins), because population studies have shown that key escape mutations are enriched in individuals with a corresponding class I HLA allele.[56–58] Given the significant differences between HCV genotypes at the amino acid level (cited as up to 30%), cross-genotype immunity may be difficult to achieve.[32,59–61]

T-cell exhaustion occurs as effector T cells become progressively less functional over time in the face of continued antigenic load, despite preservation of the cognate antigen. Cross-sectional studies have shown decreases in total numbers of T cells and functionality (largely their capacities to proliferate and secrete cytokines) in cases of persistent HCV infection.[62–64] Several T-cell markers have been identified in the mouse model of chronic lymphochoriomeningitis virus infection, including high levels of programmed death 1 (PD-1).[65] Recent studies have extended these findings into human viral infections, including HIV-1[66–68] and HCV.[69–73] Because PD-1 is characteristically up-regulated on virus-specific $CD8^+$ T cells in patients with chronic viremia for both HIV and HCV, it is hypothesized that modulation of PD-1 or its ligands increases T-cell function and perhaps helps control viral load in chronic disease.[74,75] Whether these observations from in vitro or ex vivo experiments can be exploited in vivo without inducing autoimmunity in humans remains to be determined. Moreover, PD-1 is not the only marker that signals dysfunction in virus-specific T cells (other examples may be CTLA-4 and TIM-3),[76,77] and modulation of a single pathway may not be enough to reverse T-cell dysfunction[74] and consequently lower in vivo viral loads after established chronic infection. Despite these caveats, reversing counterregulatory pathways induced during chronic infections remains a promising avenue for immunotherapeutic strategies, as evidenced by a recent proof-of-principle study in the SIV model.[78]

In addition to the internal pathways within virus-specific T cells described previously, a variety of other cell subsets are responsible for their regulation, including dendritic cells responsible for their generation[79] and T regulatory cells that counteract inflammatory responses.[80] The function of plasmacytoid dendritic cells that secrete IFN-β in chronic infection may be impaired, although data on dendritic cell impairment in HCV infection are conflicting[81–84] and more studies of dendritic cell function during acute infection and in the setting of coinfection are needed. Regulatory T cells are induced by each of these chronic viral infections and produce inhibitory cytokines such as interleukin (IL)-10 [85] that reduce proinflammatory cytokine secretion. Regulatory CD4 T-cell subsets that express the transcription factor forkhead box P3 (FOXP3) play key roles in both autoimmunity and viral infection, including that caused by HCV.[86–88] FOXP3+ regulatory T-cell subsets are altered in HIV-1 infection, but the directionality of the effect is controversial[89,90]; further investigations are needed to understand how they may influence the pathogenesis of HCV, especially within the liver. Furthermore, CD8 T cells that secrete IL-10 and TGF-β in an antigen-specific manner have been detected.[91,92] While the ability of these cells to dampen the immune system is beneficial in the short term to avoid overzealous cellular destruction, they may also play a role in the establishment of persistence and fibrosis within the liver,

especially because TGF-β serves as an activator of hepatic stellate cells, the principal source of fibrinogen within the liver.

Ultimately, generation of an adaptive immune response against HCV is relatively delayed compared with that of other acute infections, possibly because of the tolerizing effect of adaptive responses primed in the liver.[93] This delay in adaptive immunity has been linked to outcome in the chimpanzee model[94] and may be linked to events of the innate immune response. Pathways linking innate and adaptive immunity are incompletely understood in chronic viral infections but will likely yield insights into the constitution of effective immune responses.

Parallels between the specific immune response to either HCV or HIV-1 abound, but several differences should be noted. First, specific T-cell responses are found at much higher frequencies against HIV-1 compared with HCV, especially when compared within the same individuals.[95] A surprisingly high frequency of activated HIV-1–specific cells can be found in the setting of high HIV-1 viral loads,[96,97] whereas HCV-specific cells are relatively infrequent in those with chronic HCV. Second, the tropism of the viruses as well as the sites of infection likely influence the respective T-cell responses, because HCV does not primarily infect CD4 T cells and HIV-1 has not been conclusively shown to replicate within the liver. Studies have suggested that HIV-1– and HCV-specific CD8 T cells have distinct phenotypes (with HCV-specific cells skewed toward a “central memory” phenotype).[98] Further understanding of these differences may be highly relevant to what makes up an effective immune response.

HCV/HIV-1 Coinfection: The Sequence of Events

After reviewing how persistent RNA viruses such as HCV and HIV-1 evade the immune system, we next discuss why HIV-1 coinfection is associated with a higher likelihood of persistent outcome. The immune response in the context of coinfection with HIV and HCV is complex and differs based on the order of infection.

HCV Followed by HIV-1: Injection Drug Users and Blood-borne Infection

Epidemiologic studies have shown that HCV has a greater likelihood of transmission via a blood-borne route (such as by exposure to blood products or injection drug use) than HIV-1. There is an approximately 10-fold greater risk of HCV transmission after needlestick exposure compared with HIV-1[99] and a much higher prevalence of HCV than HIV-1 among injection drug users, possibly related to the greater concentrations of HCV than HIV-1 in a given volume of blood. Therefore, while cotransmission of both viruses can occur, coinfected individuals with blood-borne exposures were usually infected first with HCV, often years before HIV-1 infection.

Early cross-sectional studies that included mostly injection drug users showed that there is a higher rate of chronic HCV viremia among individuals who are coinfected with HIV-1 compared with those infected with only HCV. Higher rates of HCV persistence were inversely correlated with $CD4^+$ T-cell counts.[100] However, if the injection drug users were infected with HCV years before HIV-1, how could spontaneous clearance versus chronicity of HCV be affected by HIV-1, a much later event?

This question was addressed by a cross-sectional study that included 47 individuals who had spontaneously cleared HCV in the absence of anti-HCV therapy, 30 of whom were coinfected with HIV, and analyzed HCV-specific $CD4^+$ T-cell proliferative responses,[101] a hallmark of spontaneous clearance[62] that is absent in HIV-1/HCV–coinfected persons (particularly in those who have had very low nadir $CD4^+$ T-cell counts). When 6 of the

coinfected individuals faced recurrent HCV infections, their eventual outcome was chronicity. Virus-specific responses declined when measured longitudinally and the degree of immunosuppression at the time of recurrent HCV was related to the eventual viral load.[101] It was concluded that the secondary (or protective) immunity observed in other longitudinal cohorts[41,42] was missing from those with HIV-1 infection because of significant immunosuppression (determined by $CD4^+$ cell depletion). Although the mechanisms of $CD4^+$ cell depletion were not perfectly analogous between studies, these findings were consistent with those from a HCV rechallenge study in chimpanzees; depletion of all $CD4^+$ cells (and thus $CD4^+$ cell-mediated responses) using monoclonal antibodies resulted in prolonged hepatitis C viremia and viral escape from $CD8^+$ cell responses upon rechallenge.[43] Thus, loss of secondary immunity against HCV provides a possible explanation for how coinfection with HIV-1 results in a higher persistence rate of HCV, even in patients who were not infected with HIV-1 when they were first infected with HCV (Figure 2*A*). Therefore, coinfected patients who are negative for HCV RNA and have been given antiretroviral therapy at an earlier stage in their HIV disease should be able to preserve HCV-specific immune responses and be partially protected against reinfection.

Coinfected patients with chronic HCV infections have higher HCV titers when compared with individuals infected with only HCV. A study of sera collected from hemophiliac patients before and after HIV-1 seroconversion showed that viral loads increased by a significant amount following HIV-1 infection and more rapidly than in those who remained HIV-1 negative.[102] This increase occurred before $CD4^+$ T-cell numbers began to decline significantly, so other early effects on the immune system mediated by HIV-1 infection might be responsible for higher hepatitis C viremia in coinfected individuals. Later, as peripheral $CD4^+$ cells counts decline, there could be a loss of HCV-specific antibody responses[103,104] as well as functional HCV-specific $CD8^+$ T-cell responses.[105,106] However, HCV-specific $CD4^+$ and $CD8^+$ T cells, as currently measured, might not be linked to the viral set point. This is because HCV-specific T-cell responses are already significantly reduced in patients with chronic HCV and the magnitude of the specific immune responses against HCV in patients in the chronic phase does not correlate with viral load. The lack of correlation may relate to difficulties in measuring immune function at the site of infection (the hepatocyte), because most studies have relied on measurements either on intrahepatic lymphocytes that were expanded in vitro or on peripheral blood mononuclear cells. Ultimately, the basis for the magnitude of the HCV titer set point in each patient with a chronic infection is unknown[107]; it is likely to be related to contributions from the innate and adaptive immune systems, which in the case of coinfection are then modulated by many factors, including both HIV-1 and aging.[108,109] Further investigations understanding the perturbations induced by HIV-1 infection will improve our understanding of the mechanisms that lead to the high viral titers in coinfected patients, an issue of prime importance because these affect responsiveness to IFN-based treatments.[2]

HIV-1 Then HCV: HCV Transmission in HIV-1–Infected Men Who Have Sex With Men

Transmission of HCV is far less efficient via sexual exposure than via blood-borne exposure, whereas HIV-1 is adapted to cross the mucosa found at genital and rectal surfaces. Thus, the prevalence of HCV is far lower among those who become infected with HIV-1 by sexual risk behaviors than blood-borne exposure.[110] Numerous out- breaks of HCV infection have been reported throughout Europe and the United States among HIV-1–infected men who have sex with men (MSM).[111–117] Studies of these outbreaks have provided insights into the natural history of HCV in the context of preexisting HIV-1 infection, which may be relevant to the immunopathogenesis of coinfection.

These outbreaks were initially reported from sexually transmitted disease clinics, based on results of liver function testing. Epidemiologic studies have shown that HCV infection is

associated with sexual risk-taking behaviors that include a high number of partners, a greater likelihood for engaging in group sex, sexual acts that involve trauma, and higher rates of past sexually transmitted infections.[116] One study reported that only 17% of HIV-1–infected MSM in London who were infected with HCV reported injection drug use, suggesting that percutaneous transmission is not primarily responsible as a route of transmission.[116] HCV acquisition is also associated with higher rates of noninjection drug use (ie, 3,4-methylenedioxymethamphetamine [Ecstasy], crystal methamphetamine); it is not clear whether use of "party" drugs increases viral transmission independently of sexual risk behaviors.

The epidemic of HCV infection in MSM has occurred among HIV-1–infected individuals rather than HIV-1–negative MSM. Although HIV-1–infected MSM might engage in higher-risk practices, there are additional biological explanations for the increased HCV infection rate in this population. Source-related issues might increase transmission, because HIV-1/HCV– coinfected individuals have higher HCV viral loads than those with HCV alone. Recipient-related issues such as practices that cause trauma to mucosal surfaces and changes in local mucosal immunity that are present during early stages of HIV-1 infection might also facilitate HCV transmission. Furthermore, HIV-1 and SIV deplete $CD4^+$ T cells of the gastrointestinal tract before those of the peripheral blood.[118,119] This lack of mucosal defense could promote HCV transmission, even when those exposed are receiving antiretroviral therapy, which only partially reverses this defect.[120] Depletion of $CD4^+$ T cells from the mucosa could account for the increase in HCV infection among HIV-1–positive MSM, as compared with lower rates of infection in those who are HIV-1 negative but engage in similar practices.

Although HIV-1 infection seems to promote transmission of HCV, data on spontaneous clearance rates in HIV-1–positive MSM vary, ranging from 5% to 25%.[121,122] Higher $CD4^+$ T-cell counts were associated with spontaneous clearance of HCV[121] and HCV-specific T-cell responses were reported in 4 of 4 individuals tested,[123] suggesting no major defects in the ability of HIV-1–infected individuals to generate immunity against HCV. Although coinfected individuals usually have persistent HCV infections, spontaneous HCV clearance has been observed in these patients, indicating that HIV-1 infection alone does not preclude vaccine-induced HCV-specific immunity. However, one study showed that reduced $CD4^+$ T-cell responses against HCV in patients with HIV-1 were associated with a high rate of HCV persistence (Figure 2*B*).[122] In a small study, biopsy analyses revealed a high prevalence and degree of liver fibrosis among HIV-1–positive individuals who were recently infected with HCV.[124] Studies of larger cohorts are needed to define the progression and pathogenesis of HCV-related fibrosis in HIV-1–infected MSM, especially due to potential confounding factors such as exposure to concomitant illicit drugs, alcohol, and antiretroviral medications.

HIV-1–negative[4,125] and HIV-1–positive patients with acute HCV infections have high rates of response to IFN-based therapies (59%–90%).[114,115,121,126,127] Among coinfected individuals, this differs from the treatment response rates of those with chronic-phase HCV infections, especially for genotypes 1 or 4 (sustained virological response rates to the combination of pegylated interferon and ribavirin range from 14% to 44%), despite the more intensive and prolonged regimens used to treat patients with chronic compared with acute disease.[2] The mechanisms that underlie the increased treatment response among patients in the acute phase remain unclear but could be related to certain unique characteristics of acute infection, such as the presence of more vigorous immune responses, lower HCV viral set points, and lower diversity and complexity of viral quasispecies.[4,128]

Secondary Immunity or Therapeutic Vaccines for HCV/HIV-1–Coinfected Individuals

Preventive and therapeutic vaccines could be developed for coinfected individuals (whether first infected with HIV-1 or HCV). Therapeutic vaccines, which are designed to increase immunity against a virus, would activate $CD4^+$ helper T-cell responses; $CD8^+$ T cells are also likely to be necessary. For a therapeutic vaccine to be effective, it would need to overcome the high HCV titers observed in coinfected patients and be potent enough to avoid immediate viral escape via mutations. For preventive vaccines, the best strategy might be to increase anti-HCV immunity in patients who have cleared the virus or to induce protective immunity against HCV in those who are HIV-1 positive and at risk for acquiring HCV.

The recent failure of an adenovirus-based vaccine strategy designed to elicit $CD8^+$ T-cell immunity against HIV-1 infection could dampen enthusiasm for similar approaches to prevent HCV infection. Despite demonstrated immunogenicity, a higher number of HIV-1 infections were observed in the vaccinated group compared with the placebo group.[129] A recently developed adenoviral vector– based prophylactic vaccine against HCV could be more effective than the HIV-1 vaccine,[45] because spontaneous HCV clearance is achieved in a greater proportion of infected individuals (20%–50%); in contrast, the “elite controllers” represent only ~0.3%– 0.5% of HIV-1–infected individuals.[3] Moreover, the levels of cell-mediated immunity by IFN-γ ELISpot between individuals who have cleared HCV infection and those with chronic infection are clearly different in magnitude from each other, whereas between patients with HIV-1 that progress to AIDS and those that control the infection levels of cell-mediated immunity are often similar.[63,130]

The level of cell-mediated immunity might not be the only factor that determines HCV vaccine efficacy; $CD4^+$ and $CD8^+$ T-cell responses are required, but viruses can still escape immune detection via mutation. Due to the immense diversity of HCV (even greater than that of HIV-1), it is likely that prophylactic or therapeutic vaccines based on T cells will be genotype specific. In addition to quantity of T-cell responses, their quality, timing, and location are each of likely importance.[94,131–133] An ideal T cell may need to produce multiple antiviral cytokines, have ample proliferative capacity, and be at the “right time” and “right place” to be effective. In regard to the timing and location of T-cell responses, improving our understanding of the mechanisms that underlie the delay in the onset of the acquired immune response against HCV (the link between innate immunity and acquired immunity) and the mechanisms that govern the homing of vaccine-induced T cells (including route of administration) after viral challenge are also relevant to effective vaccines. Ultimately, the ideal HCV vaccine for HIV-1–infected individuals would probably need to be administered to patients on highly active antiretroviral therapy, so that immunity may be generated without direct interference from HIV-1 infection and in the presence of ample CD4 T-cell help.

Pathogenesis of Accelerated Liver Disease in Patients With HIV-1/HCV Coinfection

Many studies have shown that fibrosis progresses more rapidly in coinfected than mono-infected patients, leading to increased rates of cirrhosis and complications.[134,135] A recent longitudinal study supported these findings, although the phenomenon of accelerated fibrosis is not universal, because progression of fibrosis by serial biopsies is highly variable.[136] Although the immune system is likely to be involved in the fibrosis related to HCV, immunosuppression does not ameliorate fibrosis but accelerates it. Thus, HIV-1–induced immunosuppression parallels the accelerated fibrosis observed in patients with HCV following liver transplantation, who are also immunosuppressed.

The acceleration of liver disease in coinfected patients is a challenge to study because of the lack of a suitable animal model for HCV-related fibrosis; only some HCV-infected chimpanzees develop fibrosis over an extremely long period.[137] Human liver studies have been hampered by the limited frequency of sample collection and small amounts of liver tissue available, except in postmortem or explant situations. Experiments measure only a limited set of parameters, although there are many interrelated factors that potentially contribute to pathogenesis. Moreover, a biopsy represents a single snapshot of the liver; the events occurring at the time the sample was collected do not represent the whole course of a disease, which takes years to decades to develop. A parameter measured at one point in time, in a cross-sectional fashion, may not be expected to statistically correlate with an outcome that takes years to decades to develop. With these experimental and conceptual limitations in mind, Figure 3 shows pathways that have been proposed to accelerate fibrosis in coinfected patients. These include direct viral effects, dysregulation of the immune system toward a profibrotic state, and other metabolic pathways that lead to liver toxicity and processes such as steatosis and insulin resistance.

Direct Viral Effects

Although HCV viral titers are particularly high in the presence of HIV-1, a direct correlation of fibrosis with viral titers has not been confirmed.[138] Histologic variants in liver biopsy specimens of coinfected individuals have been observed that indicate direct cytopathic activity of HCV in patients with HIV-1, although this histology is unusual.[139] Some studies indicate that HCV can interact directly with the immune system; the HCV core, NS3, and NS5 proteins exert a variety of effects, in vitro, on the innate or adaptive immune system.[14,16,17,140 –142] It is not clear if these interactions occur in vivo or how they would be altered in coinfected patients. Hepatocytes have not been found to be coinfected by the 2 viruses, so a “unified theory” that would explain the pathogenesis of coinfection via intracellular interactions between HIV-1 and HCV proteins is not likely.

It has been proposed that HIV-1 is present in the liver and can promote fibrosis,[143,144] although it is more likely to act through indirect effects on hepatocytes. CCR5 and CXCR4 are coreceptors for HIV-1 that are expressed on hepatocytes and other liver resident cells. Polymorphisms in these receptors may affect the pathogenesis of HCV,[145,146] but the HIV-1 receptor CD4 is not highly expressed on hepatocytes. Experiments using in vitro models have suggested that the HIV-1 viral envelope glycoprotein gp120 can directly promote hepatocyte apoptosis[147] and result in higher viral loads by induction of TGF-β, a cytokine that dampens the immune response and promotes fibrosis and transformation toward hepatocellular carcinoma.[148,149]

Dysregulation of the Immune System

Shifts in the balance between T-helper (Th) 1 and Th2 cell activities have been postulated to be relevant to the pathogenesis of HCV. In one model, the relationship between the immune response and fibrosis involves induction of a Th2 cell response.[150] This response is mediated by cytokines such as IL-4, IL-5, and IL-13, which together with TGF-β promote collagen deposition by fibro-blasts. To counteract this process, IFN-γ, despite being proinflammatory, is antiviral and antifibrotic, whereas IL-10 is anti-inflammatory and antifibrotic. However, the perturbations of the immune system induced by HIV-1 are myriad and cannot be defined as predominant Th1 or Th2 responses.[151] We will review several aspects of the immune system that are dysregulated during HIV-1 infection and that could be relevant to accelerated liver disease (see Figure 3).

The hallmark of HIV-1 disease progression is $CD4^+$ T-cell depletion, which correlates with the risk for opportunistic infections and with worsened liver disease. Accelerated fibrosis is

most pronounced when peripheral blood $CD4^+$ T-cell counts are decreased.[152–156] Because $CD4^+$ T cells have critical roles in the support of both humoral[104] and the cytotoxic T-cell responses, their loss signals dysregulation of these arms of the immune system. Chronic antigen stimulation leads to T-cell exhaustion and direct killing of $CD4^+$ T cells (especially those with an activated phenotype, which would be expected at the site of infection and are preferentially infected by HIV-1) results in a "double hit" to antigen-specific $CD4^+$ T cells. The end result is extremely low or absent ex vivo HCV-specific $CD4^+$ T-cell responses in coinfected individuals with chronic HCV outcomes.[95,101,157–159] Canchis et al observed profound periportal loss of $CD4^+$ T cells in liver resident lymphocytes when examining the histology in coinfected individuals,[160] and other studies have suggested that HCV is associated with a greater degree of lymphocyte apoptosis in coinfected patients compared with those with HIV-1 alone.[161,162] Despite the hypothesized higher susceptibility to apoptosis of CD4 cells when resident in the liver, these cells can be recovered from liver-infiltrating lymphocyte specimens after antigen stimulation and culture for weeks in vitro, indicating that they are not necessarily completely deleted.[163,164]

Measurement of IFN-γ secretion of peripheral blood mononuclear cells in coinfected patients, via an ELISpot assay with peptides from an HCV genotype 1a strain, revealed a strong positive correlation between numbers of peripheral $CD4^+$ T cells and the total number of functional $CD8^+$ T cells specific for HCV (but not HIV-1 or Epstein–Barr virus).[105] Similarly, another study that utilized an analogous assay found reductions in IFN-γ secretion by $CD8^+$ T cells as $CD4^+$ T counts declined.[106] Together, these studies suggest that HCV-specific $CD8^+$ T cells are more sensitive to the helper cell environment than those specific to other viruses, and the relative lack of production of virus-specific IFN-γ (an antifibrotic cytokine) could be related to disease pathogenesis.[165,166] Other defects in $CD8^+$ T-cell function may also be present in coinfected individuals.[133,167]

In addition to the hypothesis that HIV-1 could have a direct role in promoting fibrosis in the liver, it is likely that immune activation by chronic HIV-1 infection could adversely affect the liver. HIV-1 activates the immune system by several mechanisms, such as direct activation by single-stranded HIV RNA of TLR, which then activate lymphocyte or dendritic cell subsets.[17,168,169] The results include polyclonal B-cell activation, increased T-cell turnover, and increased expression of various activation markers on $CD4^+$ and $CD8^+$ T cells.[170] This immune activation can predict $CD4^+$ T-cell depletion independently of viral load and is therefore believed to be crucial for HIV pathogenesis and disease progression.[171–173] In models of SIV infection, immune activation occurs in infected macaques but not in sooty mangabeys, which usually do not experience progressive immune destruction.[174] Changes in the cytokine milieu induced by immune activation could have relevance to inflammation and fibrosis in the liver. One cytokine that may be important is IL-7. IL-7 is required for maintenance of T-cell memory in the mouse model of lymphochoriomeningitis virus infections, where it sustains continued T-cell proliferation in the absence of antigen (termed homeostatic proliferation). In mouse hepatocytes, IL-7 has been recently described to be differentially regulated, challenging the previous notion that IL-7 was constitutively expressed in tissues.[175] Intrahepatic variation in IL-7 secretion and/or disruption of this IL-7 signal could therefore be linked to T-cell dysfunction.[71,176–180]

Some researchers propose that bystander activation of T cells that are not specific for HCV could be relevant to coinfection. Coinfected individuals have a greater proportion of their peripheral blood $CD8^+$ T cells specific to HIV-1 than to HCV[95,105]; these cells are present at relatively high numbers in coinfected patients, even when $CD4^+$ T cells are depleted during progressive HIV-1 infection.[97] HIV-1–specific T cells may be particularly susceptible to CD95/Fas-mediated cell death.[181] Activated HIV-1–specific $CD8^+$ T cells have been linked to the distortion of lymph node architecture and fibrosis observed in patients with

progressive HIV-1 infection[182]; one recent study reported finding these cells in the livers of coinfected individuals.[183] Therefore, activated cells that are not specific to HCV might be attracted to the liver via a bystander effect of chronic inflammation and contribute to fibrosis after apoptosis (see the following text) and release of profibrotic cytokines.[184]

A Punch to the Gut by HIV-1

As mentioned, recent models of HIV-1 immunopathogenesis have focused on the massive depletion of lymphoid tissue associated with the gastrointestinal tract, the largest lymphoid organ, leading to disrupted epithelium and increased microbial translocation.[9] The recent "rediscovery" of this enteropathy has led to further seminal insights into the pathogenesis of HIV-1. This effect is detected early in disease[118,185] and results in loss of local CD4+ T cells.[186] Furthermore, in SIV models, there is selective loss of CD4+ cells that secrete IL-17 (termed Th17 cells), a proinflammatory cytokine that has an important role in host defenses against intestinal bacteria[187,188] and possibly viruses such as HCV.[189]

In the gastrointestinal tract, this CD4+ cell depletion enteropathy leads to direct immune activation as microbial products, particularly lipopolysaccharide (LPS), enter the bloodstream and correlates with eventual disease progression.[190] LPS can increase hepatic fibrosis in animal models and has effects on Kupffer cells within the liver that would promote fibrosis.[191] A recent study extrapolated these findings to HIV-1/HCV–coinfected individuals with paired biopsies, finding a correlation between increased levels of LPS and other associated markers with liver disease progression (see Figure 4).[156] If increased LPS levels are related to the cause rather than the effect of advancing fibrosis, these findings could support novel approaches to treating liver disease in coinfected individuals, such as by eliminating harmful bacteria (such as with probiotics) and targeting LPS or its downstream effects.

Apoptosis and Liver Fibrosis

Inflammation within the liver can increase the susceptibility of intrahepatic lymphocytes, hepatocytes, and/or hepatic stellate cells to apoptosis. While induction of apoptosis of activated hepatic stellate cells, the predominant fibrogenic cell in the liver, may be beneficial,[26] overall the continuous cycle of cell death and regeneration among lymphocytes and hepatocytes is likely to promote fibrogenesis. This process involves tumor necrosis factor α activation of the Apo-1/Fas pathway, which likely contributes to HIV-1 and HCV pathogenesis.[192,193]

Another pathway that could mediate the negative effects of HIV-1/HCV coinfection on liver fibrosis is the tumor necrosis factor–related apoptosis-inducing ligand (TRAIL), also called Apo-2L, which induces apoptosis in transformed cells. TRAIL, depending on its subtype, induces apoptosis in normal human hepatocytes,[194] but its effects are more pronounced in inflammatory conditions, such as during HCV infection[195]; TRAIL is up-regulated by TGF-β.[196] $CD4^+$ T cells are more susceptible to TRAIL-induced cell death, possibly induced by IFN-β in HIV-1–infected individuals,[197] which is in turn associated with increased levels of circulating TRAIL.[198] The combination of chronic HIV-1 infection and HCV-mediated inflammation could produce an environment of increased levels of TRAIL and susceptibility of cells (stellate cells, lymphocytes, and hepatocytes) to TRAIL-mediated apoptosis within the liver.[199–201] Human hepatoma cell lines that sustain HCV subgenomic replication and express the E2 protein are protected from TRAIL-mediated apoptosis, suggesting a viral mechanism to spare HCV-infected cells.[202]

Studies in mice that are depleted of $CD4^+$ cells and infected with lymphochoriomeningitis virus have shown that a subset of $CD8^+$ T cells secrete soluble TRAIL and are of a

"helpless" phenotype, displaying reduced proliferative capacity when they encounter secondary antigen.[203] If rendered TRAIL deficient, $CD8^+$ T cells no longer exhibit this phenotype, suggesting that blockade of TRAIL or its downstream pathways could be beneficial to the function of these helpless $CD8^+$ cells.[204] It will be interesting to determine whether $CD8^+$ T cells primarily express TRAIL within the intracellular inflammatory milieu of an HCV-infected liver and whether TRAIL blockade can restore T-cell function and reverse hepatotoxicity.[205]

Other Factors That Promote Fibrosis: Steatosis, Apoptosis, and Oxidative Stress

Metabolic factors have been proposed to have important roles in the pathogenesis of HCV-mediated liver disease, particularly cases of insulin resistance and nonalcoholic liver steatosis (Figure 3).[206] Direct viral effects and chronic inflammation could contribute to the development of these metabolic syndromes,[207] although the exact mechanisms have not been elucidated. HCV infection has an independent association with the development of insulin resistance and type 2 diabetes.[208–210] Factors that lead to steatosis in the absence of alcohol could include the direct interference of HCV with lipid metabolism[211–213] and the increased sensitivity of intrahepatic lymphocytes and/or hepatocytes to apoptosis.[214–218]

To complicate the picture, chronic HIV-1 infection itself induces a host of metabolic abnormalities, including glutathione deficiency, which could predispose T cells to apoptosis via enhanced susceptibility to oxidative stress[219] and could have relevance during chronic HCV infection of the liver.[220] Furthermore, steatosis and diabetes are each potential side effects of HIV-1 therapy.[221] In coinfected patients, risk factors for hepatic steatosis include use of certain nucleoside analogues (particularly stavudine), HCV genotype 3 infection, high body mass index, and the degree of inflammation score.[222–224] Because steatosis and insulin resistance are each associated with disease progression and poor treatment outcomes, future studies will focus on further understanding of mechanisms that promote and interventions that address these cofactors.[225]

Addressing Coinfection by Treating HIV-1

Regardless of the mechanisms that contribute to the accelerated fibrosis observed in patients with HIV-1/ HCV coinfection, one available therapeutic approach is to reverse the $CD4^+$ cell depletion, apoptosis, and immune dysregulation that accompany chronic HIV-1 infection. HIV-1 can be suppressed via antiretroviral drugs; these therapeutics do not usually reduce HCV viremia,[226] which is not surprising because most immunocompetent individuals cannot control HCV. Nevertheless, antiretroviral combinations that suppress replication of HIV-1 restore $CD4^+$ T cells (and possibly HCV-specific T-cell responses), reduce immune activation, preserve Th17 responses,[227] and reduce HIV-1–specific $CD8^+$ T-cell responses.[97] Lower plasma levels of HIV-1 have been associated with reduced hepatocyte proliferation in histologic samples[160] and lower soluble levels of TRAIL.[198] Although more studies are needed, HCV/HIV-1– coinfected individuals who are long-term nonprogressors (have not experienced a progressive decline in the $CD4^+$ cell count) or have factors associated with this phenotype (such as concurrent infection with another flavivirus, GBV-C) might have more vigorous immune responses[228] or improved outcomes.[229] Interrupting the processes that mediate HIV-1 progression might be beneficial for coinfected patients (Table 2).

By a combination of mechanisms, suppression of HIV-1 via antiretroviral therapy could slow fibrosis progression rates[230] and prevent adverse liver-related outcomes.[231] Recent HIV-1 treatment guidelines suggest that HCV coinfection might present a situation under which antiretroviral therapy should be considered, independent of $CD4^+$ cell criteria, which are otherwise used to determine initiation of treatment.[232] By contrast, it should be noted

that antiretroviral therapies do not lower HCV titers,[226] can induce steatosis, and are often hepatotoxic, particularly in coinfected patients.[233,234] Postulated mechanisms of hepatotoxicity include increased hepatocyte sensitivity to direct drug effects and/or inflammatory mediators related to immune reconstitution against HCV.[235]

Is It a Two-Way Street—Possible Effects of HCV on HIV-1 Disease Progression?

Although there are many effects of HIV-1 on HCV disease progression, what are the reciprocal effects of HCV on HIV-1 disease progression? HCV coinfection has been reported to have a modest negative effect on the magnitude of $CD4^+$ T-cell reconstitution following antiretroviral therapy in some cohorts[236]; this might result from a direct effect of HCV on $CD4^+$ cell apoptosis,[161] cirrhosis-induced effects on $CD4^+$ T cells that are independent of HCV,[237] or increased immune activation.[170] Ultimately, the degree of this effect might not be of substantial clinical significance; studies have shown mixed results regarding the overall effect of HCV on HIV-1 disease progression.[238–240] At present, the overall literature suggests that the major contribution of HCV to mortality of coinfected individuals is attributable to accelerated liver disease and not increased AIDS-related complications.

Future Directions

Better tools and conceptual advances are needed to determine the interactions between HIV-1 and HCV and the immune responses to each pathogen. Although studies in chimpanzees have yielded many insights into protective immunity, the slow development of fibrosis in these animals[137] reduces their relevance to human infection and HIV infection of chimpanzees does not result in progressive disease. Primate models that are susceptible to infection with SIV are not susceptible to HCV. Until a robust small animal model of coinfection is developed, only human studies can be performed.

In the short term, research can prioritize the effects of HIV-1 on the liver, especially on the various populations of liver-resident cells described in this review. Broader studies regarding the genetic determinants of HCV and HIV-1 clearance could identify additional mechanisms of control of persistent viruses. Longer-term, larger clinical studies are needed to follow up findings from pilot studies and should include longitudinal sampling, innovative in vitro models simulating coinfection, and improved techniques. These techniques should include noninvasive markers of fibrosis, microarray analyses of gene expression patterns in liver, and improved imaging techniques (ie, confocal microscopy) to examine directly the interaction between immune cells, hepatocytes, and stellate cells.

Yearly, the HIV/AIDS vaccine budget at the National Institutes of Health exceeds $1 billion.[241] These immense resources are devoted to improving our understanding of HIV-1 disease, and many of the findings from these studies apply to HIV-1/HCV coinfection. In the field of HCV research, important topics for study include gaining better insight into the early events of HCV infection (good cell culture models are now available to answer these questions), activation of the innate immune system, the relationship between innate and adaptive immunity, the counterregulatory mechanisms that viruses use to reduce immune responses, and age-related changes in the immune system (given the effect of age on fibrosis). The development of coculture systems that model the effects of combined HCV and HIV infection of hepatocytes will advance our understanding of the pathogenesis of coinfection. Many important questions also remain about the effects of antiretrovirals, such as whether highly active antiretroviral therapy and $CD4^+$ cell repletion restore HCV-specific

immune responses and reverse profibrotic processes, in addition to mechanisms of antiretroviral hepatotoxicity and associated steatosis.

Because of the expense and difficulties of current therapies directed against HCV in coinfected patients, it would be beneficial to develop interventions that can induce the immune system to lower HCV viral titers before treatment with IFN-based treatments (thereby increasing the likelihood of sustained virological response) and/or retard the progression of fibrosis. Such interventions may first be tested in cancer immunotherapy trials or against HIV-1, and thus investments in these realms may benefit our ability to harness the immune system against HCV. In developed nations, coinfected patients have received the benefits of improved antiretroviral therapies and fewer have progressive HIV-1; the next frontiers include the challenges of accelerated fibrosis, poor response to IFN-based therapies, and system-related barriers that occur in HCV/HIV-1 coinfection.

Conclusions

Insights from clinical studies of HIV-1/HCV coinfection have revealed complex interactions that parallel challenges faced by health care providers. Coinfected patients experience accelerated fibrosis; expanding knowledge of the perturbations of host immunity induced by HIV-1 infection and the deleterious effects of the virus itself have relevance to the pathogenesis of HCV-related liver disease. These 2 viruses present immense challenges to the host immune response, yet some patients have been found to control both viruses. Gaining a greater understanding of the mechanisms of viral control and persistence could lead to therapeutic approaches to control these viruses in coinfected patients.

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Abbreviations used in this paper

AIDS	acquired immune deficiency syndrome
FOXP3	forkhead box P3
HIV-1	human immunodeficiency virus 1
IFN	interferon
IL	interleukin
LPS	lipopolysaccharide
MSM	men who have sex with men
NK	natural killer
NKT cell	natural killer T cell
PD-1	programmed death 1
SIV	simian immunodeficiency virus
TGF	transforming growth factor

Th	T helper
TLR	Toll-like receptor (TLR)
TRAIL	tumor necrosis factor–related apoptosis-inducing ligand

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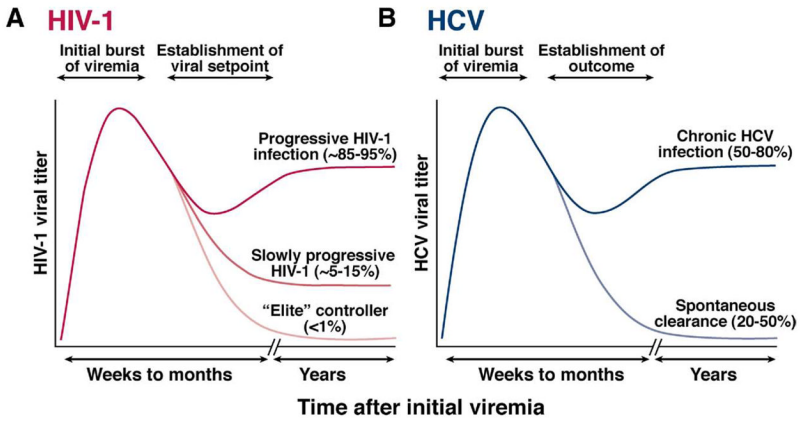

Figure 1.

Schematic representation of the outcomes of HIV-1 and HCV infection. Persistent viruses such as HIV-1 and HCV achieve high levels of chronic viral replication. The ultimate outcomes of HIV-1 and HCV infection depend on host-viral interactions. (*A*) After initial HIV-1 infection, the viral set point can vary considerably and is related to the ultimate speed of progression to AIDS. About 5%–15% of individuals experience slow progression, while a very small subset of individuals are termed "elite controllers" of HIV-1. (*B*) After HCV infection, a subset is able to control the virus over a sustained period, termed "spontaneous clearance" or "spontaneous control," but the majority (~50%– 80%) progress to chronic viremia.

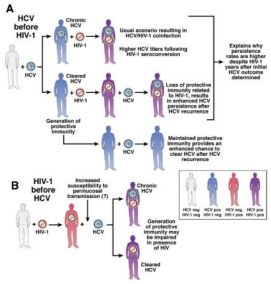

Figure 2.

Influence of the order of infection promoting the persistence of HCV in the setting of HIV-1 coinfection. Uninfected individuals are represented in *gray*, HCV antibody–positive individuals in *blue*, HIV-1 antibody–positive individuals in *red*, and dually HCV/ HIV-1 antibody–positive individuals in *purple*. (*A*) Most blood-borne exposures result in HCV infection well before HIV-1. The usual outcome is chronicity, represented in the first line. HCV titers become progressively higher after HIV-1 seroconversion. The second line represents the situation where protective immunity is generated. Progressive HIV-1 infection, signified by progressive CD4 T-cell dysfunction and depletion, may abrogate this protective immunity. When rechallenged with HCV, the likely outcome is chronicity. The third line represents a situation where HCV is cleared and HIV-1 is never contracted, and thus protective immunity is preserved. (*B*) When HIV-1 precedes HCV infection, the generation of protective immunity may be primarily impaired, thus resulting in a greater likelihood of persistent outcome. Together, this schematic may help to explain why there are higher persistence rates in coinfected individuals compared with mono-infected individuals.

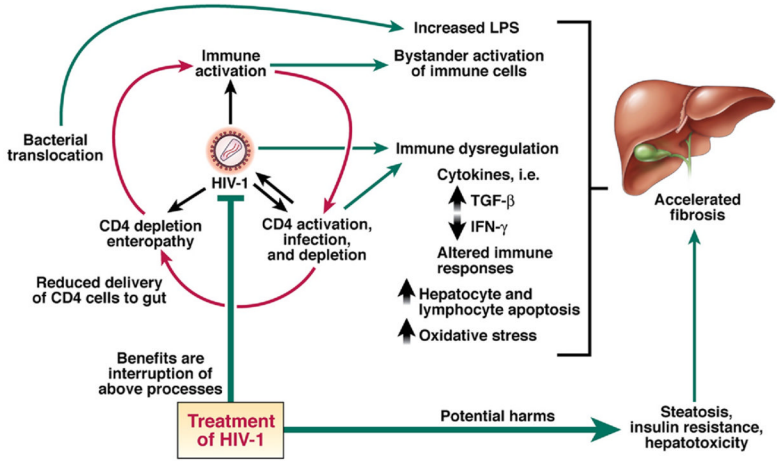

Figure 3.

Influence of HIV-1 replication and its treatment on the liver in HCV coinfection. The *red arrows* represent the "vicious cycle" of immune activation and CD4 activation, infection, and depletion, as well as effects on the gut mucosa promoting microbial translocation that are proposed to be central to the immunopathogenesis on the liver. These may affect liver fibrosis by a variety of mechanisms. Treatment of HIV-1 by antiretroviral therapy may interrupt the above processes but may introduce additional issues that are on balance negative to liver disease.

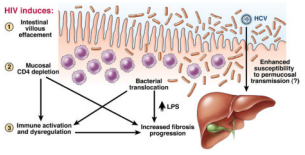

Figure 4.

Loss of mucosal lymphoid tissue related to HIV-1 infection could promote HCV-related disease. A recent study in GASTROENTEROLOGY highlights the potential role of bacterial translocation in promoting liver disease, perhaps by direct effects of LPS or indirectly by enhancing immune activation.[156] In addition, the loss of mucosal integrity can be hypothesized to enhance permucosal transmission of HCV in cases of sexual transmission, as has been detected among sexual networks in Europe.[117] Adapted with permission from Balagopal et al.[156]

Table 1

Immune Responses and Postulated Viral Evasion Mechanisms or Interactions

Host immune response	HCV	HIV-1
Innate immunity		
Activation of pathogen-associated molecular pattern via TLRs		Direct stimulation by single-stranded RNA elements[17]
Interferon signaling pathways	Core-mediated induction of SOCS3 NS3/4-mediated cleavage of CARDIF and TRIF NS5- or E2-mediated inhibition of PKR activity Reviewed in Chung et al[11]	Tat-mediated interference with PKR activity
NK cells	HCV E2 protein interference with NK receptors[21] Aberrant cross talk with dendritic cells Reviewed in Golden-Mason and Rosen[242]	Altered expression of NK receptors Aberrant or decreased cytokine secretion Aberrant cross talk with dendritic cells Enhanced apoptosis Reviewed in Ianello et al[20,243]
Regulators of adaptive immunity		
Dendritic cells	Direct infection and altered function[244]	Direct infection Decline in number and function Reviewed in Noursadeghi et al[245]
Regulatory T cells	Suppression of antiviral responses Reviewed in Billerbeck and Thimme[80]	Suppression of antiviral responses Reviewed in de St Groth and Landay[90]
Adaptive immunity		
Neutralizing antibody responses	Mutational escape Reviewed in Stamataki et al[246]	Mutational escape Glycan shielding Altered complement Loss of potency with CD4 decline Suppressed class switching Reviewed in Moir and Fauci[247]
Cell-mediated responses		
T-helper cells (CD4)	Decreased function Exhaustion Apoptosis	Direct killing Exhaustion Immune activation (producing more targets) Interference with MHC class II processing
Cytotoxic T cells (CD8)	Mutational escape Exhaustion Core-mediated down-regulation[140] Reviewed in Bowen and Walker[248]	Mutational escape Exhaustion Nef-mediated endocytosis of MHC class I[249] Vpu-mediated destabilization of MHC class I[250] Reviewed in Goulder and Watkins[251]

NOTE. This table shows various examples of viral evasion mechanisms and does not detail every possible relevant finding or cite every relevant publication; we have included reviews for the reader when appropriate for further reading.

NS, nonstructural protein; MHC, major histocompatibility complex.

Table 2

Relationship of Clinical Observations With Possible Mechanisms and Modulation by Antiretroviral Therapy

Clinical observation	Possible mechanism	Influence of HIV-1	Influence of antiretroviral therapy
Increased susceptibility to HCV infection	Donor-related		
	Higher viral loads	Increased viral load if donor is HIV-1/HCV coinfected	Antiretroviral therapy does not decrease HCV viral titers on average
	Recipient-related		
	Loss of mucosal integrity and perimucosal $CD4^+CCR5^+$ T cells	Massive gut CD4 depletion early in HIV infection	Gut-related CD4 depletion only partially restored
Increased rate of persistence	HCV before HIV-1		
	$CD4^+$ T-cell depletion, loss of secondary (protective) immunity	Direct killing by HIV	Reversal of CD4 depletion, preservation of secondary immunity
	HIV-1 before HCV		
	$CD4^+$ T-cell dysfunction	Direct killing by HIV	Reversal of CD4 depletion
	$CD8^+$ T-cell dysfunction	Related to CD4 T-cell depletion	Reversal of CD4 depletion
Increased viral loads	Loss of innate or adaptive immunity	Unclear mechanism	Antiretroviral therapy does not decrease HCV viral titers on average
Accelerated liver disease	Direct HIV-1 protein interactions	gp120 interactions	Removal of circulating HIV-1 protein
	Altered cytokine profile	Related to progressive CD4 deficiency	Reversal of CD4 depletion
	Loss/dysfunction of IFN-γ secreting HCV-specific T cells		
	Enhanced TGF-β		
	Loss of Th17 function		
	Compartmentalization of HCV-specific cells to the liver	Unknown effect	Unknown effect
	Immune activation; LPS secretion	Microbial translocation from gut	Partially restored gut mucosa
	HIV-specific T cells	Increased levels in presence of viral replication	Decreased levels of HIV-1–specific T cells
	Enhanced hepatocyte apoptosis	Up-regulation of secreted soluble proapoptotic molecules	Decreased proapoptotic molecules,
		Glutathione deficiency	Oxidative stress induced by antiretrovirals
	Hepatotoxicity		Worsened particularly by nevirapine
	Steatosis and metabolic abnormalities		Possible relationship to certain antiretrovirals (ie, stavudine)