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# REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY

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

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**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 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 ($\sim 10^9$ particles/day for HIV-1 and $\sim 10^{12}$ 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

*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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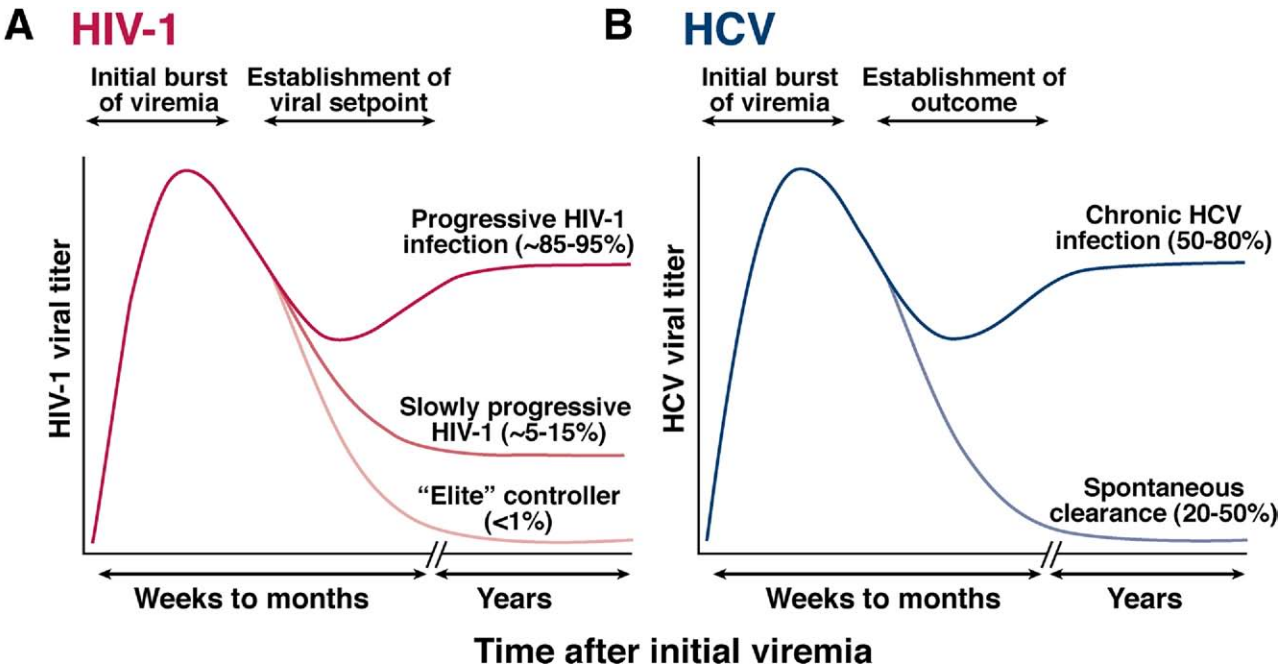


**Figure 1.** Schematic representation of the outcomes of HIV-1 and HCV infection. Persistent viruses such as HIV-1 and HCV achieve high levels of chronic viral replication. The ultimate outcomes of HIV-1 and HCV infection depend on host-viral interactions. (*A*) After initial HIV-1 infection, the viral 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.

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]