Early antiretroviral therapy: an immunotherapy to combat HCV in HIV-1/HCV coinfection

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HCV & HIV-1: two viruses traveling hand-in-hand

HCV, a *Flavivirus*, and HIV-1, a retrovirus, are genetically unrelated viruses that are similar in two primary ways. First, they share routes of transmission and are often found as companions, sharing the same human host. Second, they are both persistent viruses characterized by high plasma viremia. These traveling companions do not wear out their welcome by destroying their environs immediately, but instead insidiously reside in their host and inflict their harm over a number of years. Ample clinical evidence demonstrates that, when together, HIV-1 allows HCV to carry out its damage at an even faster rate. Since people with HIV-1 are now living longer due to antiretroviral therapy (ART), clinical interest in addressing HCV in HCV/HIV-1 coinfecting individuals has amplified markedly.

Fortunately, therapies for both HCV and HIV-1 have improved over the past decade. The practitioner now has a choice of which of these unwelcome guests to tackle first in any given patient. When one infection poses a bigger threat than the other, the choice is easy. For instance, in the case of HIV-1 'nonprogressor' status (i.e., high CD4 counts, low HIV-1 viral load) with advancing HCV-related liver disease, HCV should be addressed first. Conversely, those with minimal liver disease, but at high risk of opportunistic infections, require antiretrovirals to reverse CD4⁺ T-cell loss and restore immunity. Those patients with situations in between these extremes can represent a conundrum to clinicians.

This editorial aims to present clinical and experimental evidence relevant to the concept of ART as an 'immunotherapy' to combat HCV in

HIV-1/HCV coinfection, and proposes a perspective that earlier use of ART may beneficially alter the course of HCV-related liver disease.

Clinical evidence regarding HIV-1 influence on HCV

Since HCV is not considered a cytopathic virus, the immune response is considered the main mediator of inflammatory damage, leading to hepatic fibrosis in viral hepatitis. One could hypothesize that immunosuppression should ameliorate the disease course. This is not the case as HIV-1 has a negative effect on all stages of HCV disease: a higher rate of persistent viremia, higher serum HCV levels, and higher rates of fibrosis progression [1]. In addition, the higher viral loads are one of several barriers to effective anti-HCV treatment in this population [2]. Liver disease resulting from viral coinfections now represents the leading non-HIV-related cause of death in HIV-positive individuals [3]. Chronic HIV-1 infection, when unchecked, is an accelerant of the deleterious effects of HCV.

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What are the cofactors that accelerate HCV-related disease in those patients coinfecting with HIV-1?

While concomitant alcohol use is one obvious factor, a consensus is forming that low CD4 T-cell count is another [4]. This finding has a parallel in the post-transplant period, where HCV reinfection of the transplanted liver often results in accelerated liver fibrosis and the development of cirrhosis in a short timeframe. While the disease course may vary between individuals, those with HIV-1 and HCV on balance experience an acceleration of liver disease when compared with their counterparts infected with HCV alone. This is related to the duration of uncontrolled HIV-1 viremia and immunosuppression.

If the consequences of HIV-1 infection and CD4 depletion are deleterious in terms of HCV immunity and clinical outcomes, then it is logical

to ask whether HIV-1 suppression with ART can reverse these effects, and to further consider the benefits of ART as an immunotherapy to prevent low CD4 counts in this population.

Immunopathogenesis of HIV-1/HCV coinfection

Studies examining the immunopathogenesis of both HCV monoinfection and HIV-1 have focused on the adaptive immune response, in particular virus-specific T cells. After acute HCV infection, the appearance of these cells is temporally associated with the initial decline in viral load and their maintenance is associated with viral clearance [5]. To lend further credence to the importance of these responses, the virus has apparently evolved mechanisms that enable evasion from immune containment, including viral escape from T-cell responses [6,7].

One of the hallmarks of spontaneous recovery from HCV is a higher frequency and magnitude of T-cell responses compared with those who have gone on to chronicity [8,9]. Those with prior evidence of spontaneous control of HCV have better outcomes upon rechallenge by a new infection [10]. In rechallenge experiments in the chimpanzee model, in which either CD8 or CD4 T cells are depleted, prolonged periods of HCV viremia are observed [11,12]. Based on these observations, we conclude that the generation and maintenance of these long-lived memory lymphocytes are correlates of this secondary immunity.

How does HIV-1 coinfection affect this immunity? From a pathogenesis standpoint, HIV-1 infection results in both CD4 T-cell depletion and immune activation. Our laboratory has examined the issue of HIV-1-induced CD4 T-cell depletion and its effects on HCV-specific immunity. We have measured immune responses against HCV using a variety of techniques in a large cohort of coinfecting individuals, and included a fair number of subjects with lower CD4 T-cell counts. We found that the breadth and magnitude of HCV-specific CD8⁺ T-cell responses that produce IFN- γ depend on higher CD4⁺ T-cell counts [13]. While IFN- γ is a proinflammatory molecule, it also has antifibrotic effects; thus, loss of T cells capable of homing to the site of infection may have relevance to the increased fibrosis progression observed in this population. Furthermore, while we did not find significant frequencies of *ex vivo* circulating HCV-specific CD8⁺ T cells in persons with low CD4 counts, these responses were recoverable after short term *in vitro* stimulation of their

peripheral blood mononuclear cells with HCV peptides. Thus, these cells are not entirely absent from those exhibiting CD4 depletion due to HIV-1, but remain at low frequency [13]. This latter finding raises the possibility of restoration of T-cell immunity as one restores CD4 counts while on ART therapy.

Why are T-cell responses worth preserving or restoring? In an individual with evidence of spontaneous (i.e., natural and not treatment-induced) control of HCV, there is an important potential benefit to preserving these responses.

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In our recent study of persons exhibiting this less usual outcome of HCV, we found that those who were HIV positive had a greater likelihood of experiencing recurrence of HCV viremia than those without HIV. Those with higher CD4 T-cell counts and preserved T-cell immunity had much better control of their virus subsequent to this second HCV challenge than those with lower CD4 counts and immunity [8]. HCV-specific CD4 T cells were preserved in those with higher historical nadir CD4 counts (i.e., those with long-term non-progression and/or earlier ART before CD4 counts dropped). Loss of immunological memory specific to HCV could provide an explanation of the higher rate of persistent HCV observed in HIV-1 coinfection. Therefore, a treatment strategy that is initiated earlier than traditionally recommended should be considered in the situation of spontaneous control of HCV, with goals of avoiding low nadir CD4 counts, preserving these memory responses and preventing HCV recurrence. It does not make sense to lose naturally generated and possibly effective secondary immunity against HCV by allowing HIV-1 to go unchecked for too long.

What happens in the more usual situation, for instance in those with chronic HCV and HIV-1 who start on ART? These persons do not generally achieve spontaneous clearance of HCV upon restoration of the immune system. Rather, they experience a transient initial increase in plasma HCV-RNA levels in the first months, with a return to baseline levels over time [14]. Restoration of effective immunity would not be

expected to be a usual outcome, especially since immunity often fails even when HIV-1 is not in the picture (i.e., most people with HCV monoinfection have chronic viremia). Given that CD4⁺ T cells are a major target of HIV-1 infection and are already diminished in chronic HCV, the prospects of the restoration of HCV-specific CD4⁺ T cells are not great due to this dual insult. However, one possibility is that ART may restore more general T-cell help that supports HCV-specific CD8⁺ T cells, which, in turn, may have beneficial effects on liver histology [15]. Additional potential immunological benefits of ART include restoration of gut-associated lymphoid tissue, which may alter lipopolysaccharide levels related to the translocation of bacterial flora, and a decrease in immune activation. We hypothesize that, at the very least, effective ART will reverse negative immunologic consequences of HIV-1 and adjust a dysregulated immune system towards the HCV-monoinfected situation.

Regardless of whether restoration of HCV-specific immunity occurs, there is a growing body of clinical evidence showing that proper use of ART positively affects HCV-related outcomes. One example is a study by Qurishi and colleagues that found an expected survival benefit from ARTs among persons coinfecting with both viruses, with a more relevant finding to this discussion: an accompanying reduction in liver-related mortality.

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This survival benefit was parsed further – those on highly active therapy had the best liver-related outcomes when compared with those off therapy, while those who were on non triple-therapy regimens (with a lower likelihood of achieving virologic and immunologic responses) had an intermediate outcome [16]. Brau and colleagues measured fibrosis progression rates (FPRs) in coinfecting persons and found that those with viral suppression on ART had the lowest FPR compared with those off therapy; those who were on suboptimal ART (HIV-viral load detectable) had an intermediate FPR [17]. These studies suggest that the outcomes of interest (decreasing HCV-related liver fibrosis

progression and accompanying morbidity and mortality) are reversed based on how well one can achieve virologic suppression of HIV-1. Thus, there is evidence that ART may be acting as an immunotherapy, having no direct antiviral activity against HCV.

Picking your poison

What are the arguments against the earlier use of antiretrovirals to boost CD4 T-cell counts as a strategy to alter the course of HCV infection? The first argues that early exposure to antiretrovirals will decrease quality-of-life due to side effects and will unnecessarily increase the risk of hepatotoxicity. There is further risk if the patient takes a regimen suboptimally of resistant HIV-1, reducing treatment options in the future. My response to this argument is that while hepatotoxicity cannot be dismissed entirely, overall clinical studies show a balance towards benefits of ART, and recent consensus guidelines do not present hepatotoxicity as a limiting factor to this strategy [18]. It should be noted that our armamentarium against HIV-1 has gained several later-generation drugs that may have reduced long-term toxicities and greater barriers to the development of viral resistance.

A second main counterargument is the availability of improved anti-HCV treatments, namely pegylated IFN- α -2a and -2b, both in combination with ribavirin. When tested in persons with HIV-1/HCV coinfection, response rates as measured by viral clearance are indeed better than prior therapies, and histological outcomes, on balance, are also improved [2]. Despite these improvements, the application of interferon-based therapies has proven difficult. This is in part due to high rates of inability to complete the pretreatment work-up, contraindications to treatment and complications of therapy. One recent survey in an inner-city clinic interested in addressing liver disease in the presence of HIV-1/HCV coinfection determined that fewer than 1% of candidates completed interferon-based treatment successfully [19]. Thus, while there are improved options for the treatment of HCV in this population, some have argued that the treatment of HIV-1 may be more tolerable and have an impact on a greater number of patients [20].

Finally, one can argue that we do not have conclusive data in the absence of a randomized controlled trial examining the question of earlier ART for coinfecting patients. While CD4 T-cell depletion is associated with less HCV-specific immunity and poorer HCV-related outcomes,

studies have been cross-sectional in design and thus, may not be conclusive. Retrospective longitudinal studies on the natural history may be affected by different biases. A randomized controlled trial designed to address this issue will be difficult, if not impossible, to enroll and, given the rapidly changing options for ART, will take too long to provide useful information. Nevertheless, we do not have compelling evidence that we are likely to cause overall harm by considering ART as a valid approach to HCV-related liver disease for coinfecting persons. Rather, we have reasonable evidence that ART represents a modulation of the immune system with a positive clinical and immunological effect and therefore can be considered an immunotherapy for HCV in HCV/HIV-1 coinfecting subjects.

Conclusion & future perspective

Several directions of observational research and therapeutic trials are needed to tackle this vexing clinical problem. Intense effort should be devoted to improved experimental models of HCV that can then be applied to HIV-1 coinfection, and to explain an expanded understanding of the immunopathogenesis of coinfection with these two viruses, including the genetic and immunologic basis of clinical phenomena and application of novel therapeutics (direct molecular inhibitors of viral proteins, antifibrotic molecules and immunotherapies).

Multiple candidate drugs will be added to the anti-HCV arsenal and have generated much enthusiasm. They will eventually revolutionize this field. These include direct inhibitors of proteins critical in the viral lifecycle and initial studies show proof-of-principle of *in vivo* efficacy. That said, these drugs are still several steps from approval for HCV monoinfection and ascertaining their proper use in coinfecting populations will require even more forethought and study.

In the meantime, are we relegated to crossing our fingers and hoping for the best with the current situation, when it is unclear which of the two viruses to tackle first? For much of the time, treating HCV will not be an option, and we can have confidence that treating HIV-1, while not a cure, is an approach that may stave off negative liver-related outcomes for a period. ART represents our first immunotherapy for the management of the complex situation surrounding HIV-1/HCV coinfection, by ameliorating the immunologic lesions inflicted by HIV-1 and likely putting the brakes on accelerated liver disease progression. Thus, earlier ART should be considered for HIV-1/HCV coinfecting persons as this may buy patients time until more effective and tolerable treatments arrive on the scene.

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Executive summary

HCV & HIV-1: two viruses traveling hand-in-hand

- HIV-1 travels together with HCV due to shared transmission routes, but it is often unclear which infection should be addressed first in patients.
- HIV-1 is associated with a higher rate of HCV persistence and accelerates HCV-related liver disease, particularly at low CD4 T-cell counts.

Immunopathogenesis of HIV-1/HCV coinfection

- Spontaneous control of HCV is associated with long-lived memory CD4 and CD8 cells that may be beneficial to secondary immunity.
- HCV-specific T-cell responses are lost in HIV-1 infection when CD4 counts are depleted.
- Reversing the effects of HIV-1 infection with antiretroviral therapy restores CD4 counts and may preserve or restore HCV-specific immunity and improve HCV-related outcomes.

Picking your poison

- Antiretroviral therapy has associated risks (e.g., hepatotoxicity and resistance), however, options are improving with the introduction of new drugs.
- Current interferon-based therapy is difficult to apply broadly in this population.

Conclusion

- Antiretroviral therapy represents the best 'immunotherapy' that may act to slow down the progression of HCV-related fibrosis.

Future perspective

- Novel therapies for HCV are in the pipeline and should revolutionize our approaches to HCV in coinfecting persons.
- A better understanding of the mechanisms of accelerated fibrosis will lead to specific immune-based therapies.

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