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CO-INFECTIONS AND COMORBIDITY (S NAGGIE, SECTION EDITOR)

HIV, Aging, and Viral Coinfections: Taking the Long View

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Abstract Viral suppression of human immunodeficiency virus (HIV) with combination antiviral therapy (cART) has led to increasing longevity but has not enabled a complete return to health among aging HIV-infected individuals (HIV+). Viral coinfections are prevalent in the HIV+ host and are implicated in cancer, liver disease, and accelerated aging. We must move beyond a simplistic notion of HIV becoming a "chronic controllable illness" and develop an understanding of how viral suppression alters the natural history of HIV infection, especially at the intersection of HIV with other common viral coinfections in the context of an altered, aging immune system.

Keywords HIV · Viral hepatitis · Liver disease · HPV · Cancer · Aging · Coinfection

Introduction

Human immunodeficiency virus (HIV) disease has become a chronic condition, with a shift in all-cause mortality to non-AIDS related deaths [1]. The US Centers for Disease Control and Prevention estimates that more than half of people living with HIV infection (HIV+) in the USA are 50 years of age or older [2]. As combination antiviral therapy (cART) has altered the course of this infection, we must annotate our understanding of the natural history of HIV disease. In particular, factors that influence disease have more time to become evident, such as chronic inflammation, alterations in host defenses, cell senescence, and cumulative antiretroviral and non-antiretroviral medication-related toxicity (Fig. 1).

The HIV population is experiencing a significant disease burden from liver-related illness and cancer [3]. However, new, curative direct-acting antiviral therapies for chronic

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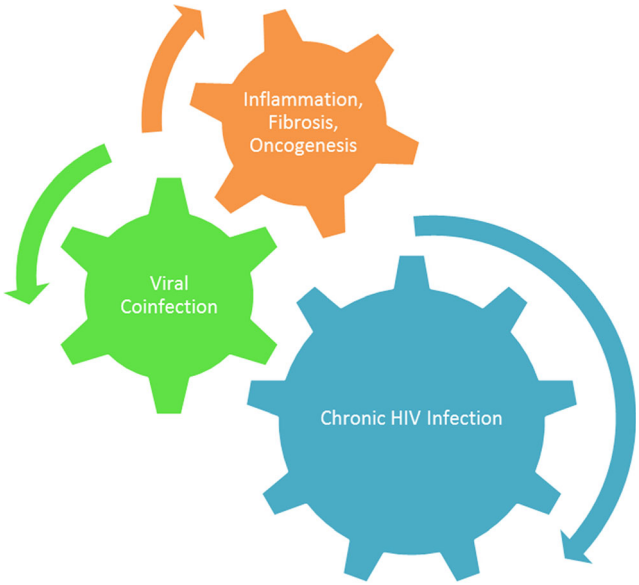

Fig. 1 Inter-relatedness of HIV infection, viral coinfection, and inflammation

hepatitis C virus (HCV) infection will likely alter the natural course of HCV-related liver disease [4••, 5••, 6••, 7••]. Consequently, clinicians are prioritizing HCV treatment in HIV+ patients to prevent accelerated progression of liver disease [8]. Curing HCV in HIV+ will help to reduce liver-related complications and prolong survival. Additionally, "precision medicine" for the cancer patient takes into account targetable genetic modifications in cancer cells [9•, 10•, 11•], but we know very little about the selective genetic pressures imposed by HIV and coinfection with oncogenic viruses, such as HCV, hepatitis B virus (HBV), and human papilloma virus (HPV). Finally, how the HIV+ host on cART handles other common viruses may also have an impact on aging. CMV-related accelerated immunosenescence in HIV+ is paradoxically accentuated by cART [12••]. As HIV infection shifts to a more prolonged disease course, we must embrace the complexity of this illness and its intersections. By doing so, we will grow in our understanding of how viral coinfection affects this unique host and we may be able to apply that knowledge to improving clinical management and developing therapeutic targets.

This review will discuss three important areas related to HIV, viral coinfections, and aging: cancer, liver disease, and accelerated immunosenescence (Table 1).

An Emerging Special Population: Cancer

Consider a Case

In late 2011, a 64-year-old African-American HIV+ male (viral load suppressed on abacavir, lamivudine, efavirenz, and raltegravir), coinfected with chronic HCV, was undergoing evaluation of a 2.5-cm left lower pole renal mass when a CT scan showed a small but enlarging liver mass. A 1.2-cm mass in the right hepatic lobe had increased in size compared to prior imaging. The lesion was radiographically consistent with hepatocellular carcinoma (HCC) based on its brisk enhancement on the arterial phase, with hypoenhancement on portal venous and delayed phases. A tissue biopsy of the mass was performed given the concern of possible metastases from the presumed renal cell carcinoma, and the absence of any clinical, biochemical, or imaging evidence of cirrhosis. Pathology was diagnostic of a small focus of moderately differentiated HCC; the background parenchyma showed stage II fibrosis. The patient underwent curative radiofrequency ablation of the lesion in early 2012. Surveillance MRI showed no recurrence at 3 months, at which time the renal mass had grown to 3.2 × 3.1 cm; this was ultimately managed with cryoablation. In late 2014, he was treated with sofosbuvir and simeprevir for 12 weeks for genotype 1a HCV (treatment naïve); his adherence was questionable, and he experienced virological relapse following treatment. Surveillance MRIs of the liver post ablation have shown no evidence of HCC recurrence.

This case highlights several key points. First, this patient developed HCC in the absence of cirrhosis, a phenomenon that has been described in HIV+/HCV+ patients, but is extremely rare in HCV+ monoinfected individuals, suggesting an accelerated path to oncogenesis [13]. Second, many cancers, including HCC, are virally mediated in HIV+ [14–16]. Third, hepatic resection for HCC and partial nephrectomy for renal cell carcinoma may have been more definitive curative options in this patient, but the presence of and stigma attached to his comorbidities may have altered his treatment course.

Cancer diagnoses in HIV+ have shifted from AIDS-defining cancers (Kaposi sarcoma and non-Hodgkin lymphoma) to non-AIDS-defining cancers [14–16]. Non-AIDS-defining cancers are now the leading cause of death in HIV+ [17••]. While much of this change has been brought about by cART and aging and survivorship of HIV+ individuals, it is important to note that there is a high prevalence of virally mediated cancers in this population, specifically HCV, HBV, and HPV-related malignancies.

HCV/HBV-Related HCC

HIV infection modifies the natural history of HCV and HBV infection and may contribute to development of HCC [18••, 19]. The effect of HIV on CD4 cells and profibrotic mediators is thought to accelerate the progression of liver disease. Reduced HCV clearance rates and higher HCV and HBV viral loads have been demonstrated in HIV+ [20, 21, 22••, 23•]. Several risk factors common in HIV+ patients further accelerate progression of liver disease, such as alcohol consumption, age at infection, and lower CD4 count [18••, 23•]. This

Table 1 HIV coinfections, alterations in natural history of disease, and associated sequelae

Infection[a]	HIV-related alteration in natural history of disease	Sequela(e)
Hepatitis C virus	Accelerated liver fibrosis; Extrahepatic end organ disease	Cirrhosis/liver cancer
		Coronary artery disease
		Diabetes
		Neurocognitive disorders
		Bone loss
		Chronic kidney disease
Hepatitis B virus	Accelerated liver fibrosis	Cirrhosis/liver Cancer
Human papilloma virus	Higher incidence and persistence of infection	Anogenital cancer
		Cervical cancer
		Oropharyngeal cancer
Cytomegalovirus	Immunosenescence	Alterations in aging
Epstein-Barr virus	Immune deficiency-related incidence	Non-Hodgkin lymphoma, Hodgkin lymphoma
Kaposi sarcoma-associated herpes virus	Immune deficiency-related incidence	Kaposi sarcoma

[a] See also Dubrow et al. [72]

accelerated hepatic fibrosis progression increases the risk of developing cirrhosis and hepatic decompensation [24, 25]. It has also been shown that HIV+ present with HCC at younger ages and with more advanced disease [26]. The pathophysiological mechanisms for accelerated fibrosis progression in coinfected people are multifactorial and may be related to direct effects of HIV and its interaction with the immune system and the hepatic milieu. HIV-related immune dysregulation, HIV-mediated depletion of CD4 cells in the gastrointestinal tract with resultant microbial translocation, HIV-related oxidative stress, and HIV-induced hepatocyte apoptosis have been implicated in the pathogenesis of progressive hepatic disease in HIV+ patients [27]. In HIV+, there are alterations in several pro-fibrotic pathways that have oncogenic corollaries. For example, in HIV+, natural killer (NK) cells are dysfunctional in their ability to induce stellate cell apoptosis [28]. HIV is also known to increase TGF-beta-1, a canonical mediator of fibrosis and oncogenesis [29]. Interestingly, toxicity of antiretroviral agents has also been implicated in liver disease and HCC risk. Ryom and colleagues have recently shown in a large European cohort that certain antiretroviral drugs were independently associated with an increase in ESLD/HCC rates, calling for further investigation into the effects of these drugs on liver function, fibrosis, and oncogenesis [30•].

Given the rapid hepatic fibrosis progression in HIV/viral hepatitis-coinfected patients and potential oncogenesis induced by HIV, HCC, a devastating disease with few effective treatments, is increasingly common among those aging with HIV [31–34]. For those without HIV, HCC is a disease of aging (median, 64 years), occurring in the context of cumulative liver injury from multiple chronic conditions (multimorbidity) [35–37]. Multimorbidity associated with HCC includes chronic HCV and HBV, heavy alcohol use, obesity, and diabetes mellitus. Of those with HCC, 90 % have advanced liver fibrosis/cirrhosis [35–38, 39••]. Less is known about HCC among HIV+. In the USA, the prevalence of HCC among HIV+ has increased 12-fold between 1996 and 2009 [32]. The US HIV/AIDS Cancer Match Study (1980–2009) found that the incidence of HCC among HIV+ has quadrupled in 3 decades and HIV+ patients have a fourfold higher risk of HCC than uninfected individuals, even after adjustment for HCV/HBV and alcohol [31]. HCC has been a particular problem among HIV+/HCV+ patients, since chronic HCV occurs in 10–30 % of HIV patients [40, 41]. HIV+/HCV+ have a fivefold higher risk of HCC than HIV+ alone [18••, 32, 42, 43].

However, many cases of HCC in HIV+ occur without HCV [26, 44–47]. The extent to which this represents silent HBV infection (e.g., isolated HBV core antibody positive) or less understood mechanisms of injury is unclear. Moreover, incident HCC is increasing at a higher rate in HIV+ than uninfected, particularly in those over 65 years of age [48••]. Consequently, HCC mortality is expected to increase dramatically with time among HIV+ patients [49••].

Chronic HBV infection is a vaccine preventable illness with a prevalence of 248 million worldwide [50, 51]. Coinfection with chronic HBV occurs in 6–14 % of HIV+ patients in North America and Europe [52, 53] and 10–20 % in Asia and Africa [54–56]. Similar to HIV, HBV is not yet

curable once chronic infection occurs. However, nucleos(t)ide analogs are highly active against HBV and are often contained in cART regimens prescribed for HIV+. HCC may occur in the absence of cirrhosis in patients with HBV due to the direct oncogenic effect of the virus [57]. Suppression of viral replication reduces the risk of developing HCC [58••]. HBV DNA levels are often higher in HIV+/HBV+ patients, and viral load must be suppressed in these patients regardless of CD4 count [59]. It is important to note that HIV+ patient with HBV+/HDV+ coinfection is at extremely high risk of developing cirrhosis and HCC [60•, 61•]. Patients with cirrhosis are advised to have abdominal ultrasounds every 6 months for HCC surveillance [62, 63••, 64]. We would advise the same surveillance regimen for those without cirrhosis with viral suppression on cART who had a baseline HBV-DNA level > 2000 IU/ml and/or significant duration of infection (over 20 years) [65••].

Reactivation or "flare" is a concern when patients are immunosuppressed as is becoming more common with the emergence of immune modulating drugs for cancers and other conditions [66••, 67••]. It is important to note that HBV reactivation in the setting of immunosuppression can occur in any prior exposed patient, including those with isolated HBV core antibody and, less frequently, in those with surface antibody. Soriano and colleagues have recently published an excellent concise review on the management of HIV+/HBV+ coinfection [68••].

Human Papillomavirus (HPV)-Related Cancers

HPV has been identified as a causal factor in oropharyngeal, cervical, and anal cancers. HPV is associated with the majority of oropharyngeal cancers in the USA [69]. Men who have sex with men (MSM) and all those with HIV infection are at increased risk of developing HPV-related cancers [70]. However, the site of cancer is important when comparing the incidence in HIV+ compared to HIV−. Risk of anal cancer is approximately 25-fold in HIV+ compared to HIV− who are not MSM and 80-fold among MSM with HIV infection [71], whereas risk of oropharyngeal cancer is estimated at sixfold higher [72]. This disparity may be due to the higher incidence and persistence of anal HPV infection compared to oral HPV infection in HIV+ [73]. Beachler and colleagues reported an 84 % anal HPV prevalence vs. 28 % oral HPV prevalence and a 12-month persistent rate of 54 % for anal HPV vs. 29 % for oral HPV in 404 HIV+ adults [73]. Factors that affect infection and persistence of oral or anal HPV infection may be related to the presence of HIV itself. Oral HPV infection was higher in HIV+ even after controlling for smoking and sexual behavior, suggesting that HIV may affect the natural history of HPV [74]. Oral HPV prevalence is associated with immunosuppression, and the odds of oral HPV are increased among HIV+ with a low CD4 count [75•]. A prospective observational cohort study by Beachler and colleagues has further delineated the natural history of HPV infection in HIV+ and HIV− patients, reporting a 2-year cumulative incidence of 34 % of any oral HPV infection in HIV+ and 19 % in HIV−. While clearance rates were high, persistence of infection for at least 2 years was noted in 35 % of prevalent infections and 7 % of incident infections. HIV infection, low CD4 count, and a higher number of oral sex partners increased the risk of incident HPV infection; older individuals, male sex, and current smokers were more likely to have persistent HPV. However, the accepted association between persistent anogenital HPV and risk of anogenital cancer may not be analogous in oral HPV and oropharyngeal cancer [76•].

The actions of HIV-1 transactivator protein (Tat) have more recently been shown to directly facilitate HPV infection. Tat is required for HIV transcription and replication [77] and has been shown to activate T-cells [78] and induce apoptosis [79]. Tat has also been shown to potentiate HPV infection [80, 81], potentially via HIV-associated disruption of epithelial tight junctions [81]. Interestingly, there have been associations between Tat and Notch1 [82], and a recent study has reported that differential activity of Notch1 promotes HPV-related oropharyngeal tumors [83•]. Notch1 signaling has been associated with the development and proliferation of multiple cancers; a recent study suggests activation of Notch1 contributes to increased expression of stem cell markers in head and neck cancers [84•].

As several genome wide association studies have demonstrated genetic variations in HIV susceptibility and pathophysiology [85], whole genome or whole exome studies are likely to offer new insights into genetic alterations that are involved in the pathways to HPV-related and other cancers in HIV+. While it is difficult to tease out the effects of non-HIV cancer risk factors in HIV+, such as smoking, alcohol consumption, and obesity, technology is rapidly evolving so that we may be able to understand the effects of epigenetic and environmental phenomena on specific, at risk populations.

HIV/HCV-coinfected Patients: Still a Special Population?

With HIV viral suppression, AIDS-related deaths have declined sharply while non-AIDS related causes of death, specifically liver related, have become more common [86]. In HIV-infected individuals, the prevalence of HCV coinfection is estimated to be at least 5 million globally [87]. Coinfected individuals experience higher rates of fibrosis, cirrhosis, decompensated liver disease, liver cancer, and death [18••, 88]. Alcohol use [89•], obesity [90•], and insulin resistance [91] have also been cited as additional risk factors for accelerated fibrosis progression in the coinfected population. The natural history of liver disease in HIV/HCV-coinfected individuals differs from the natural history of HCV monoinfected

individuals due to altered immune, metabolic, and endocrine status as well as the effects of cART. The HIV/HCV coinfected individual is also at risk for extrahepatic end organ disease, such as coronary artery disease, diabetes, neurocognitive disorders, bone loss, and chronic kidney disease. Accelerated fibrosis progression and portal hypertension are seen in the HIV+/HCV+ population, especially those with low CD4 counts (<200) [92••, 93]. Early cART initiation among HIV+/HCV+ is advised to optimize HCV treatment and to reduce the risk of progression of fibrosis [94]. Accelerated fibrosis has been reported in older HIV+/HCV+ patients, even after HCV is cured [95]. HCV infection also increased the risk of progression to AIDS and death in one large multinational seroconverter cohort study [96]. Accordingly, the IDSA/AASLD guidelines have prioritized the treatment of HCV in coinfected patients [97••], a population with higher rates of decompensation (even with HIV viral suppression) [18••], poorer survival [98], and higher rates of HCC at younger ages [26].

The HIV/HCV coinfected population has long been considered a challenging population to treat due to drug/drug interactions, adverse effects of cytopenias, and low rates of interferon eligibility. However, the new era of direct-acting antiviral (DAA) therapies for chronic HCV has sparked a revolution. These antivirals result in high (≥94 %) rates of sustained virologic response (i.e., viral cure, defined as the absence of HCV viremia 12 weeks after the end of HCV therapy) in HIV/HCV coinfected patients with typically no more than 12 weeks of treatment [4••, 5••, 6••, 7••, 99]. The PHOTON-1 study was the landmark study that assessed the efficacy of an all-oral, interferon-free regimen for HCV genotypes 1, 2, and 3 in patients coinfected with HIV [100•, 101]. SVR rates were comparable with or superior to interferon-based therapies with an all-oral regimen of sofosbuvir and ribavirin for 12–24 weeks. Sofosbuvir, a nucleotide analog inhibitor of the HCV NS5B polymerase with a high barrier to resistance, does not interact with cytochrome P450 3A4 (CYP3A4) metabolized drugs and, therefore, can be taken without modification of dose or frequency of administration. The first-generation DAAs, telaprevir and boceprevir, reacted extensively with the CYP3A4 isoenzyme, causing significant drug-drug interactions with many standard cART regimens. These drugs were given in combination with interferon and had significant toxicities with cumbersome and clinically impractical rules for stopping when further treatment was futile. The PHOTON-1 study demonstrated parity of response to antiviral therapy between coinfected patients and monoinfected patients with interferon-free regimens of shorter durations among patients taking diverse cART regimens. While regimens continue to change with the arrival of newer DAA therapies (sofosbuvir/ledipasvir, sofosbuvir/daclatasvir, elbasvir/grazoprevir, and sofosbuvir/velpatasvir), we are witnessing continued parity in SVR among HCV monoinfected and HIV/HCV coinfected patients. The reader is encouraged to visit the AASLD/IDSA guidelines website for the most up-to-date recommendations. The infectious disease and hepatology communities have highlighted the priority of treating coinfected patients, regardless of the degree of underlying liver fibrosis, at a time when the costs of these drugs are prohibitively expensive and their use is often rationed only to those HCV monoinfected individuals with advanced fibrosis. The possibility of curing HCV in HIV patients with the same ease as monoinfected patients has rendered this "special population" of HCV-infected individuals not so special any more.[101]

Studies in monoinfected patients have shown that pegylated-interferon/ribavirin-induced SVR results in a lower rate of liver-related complications [102] and all-cause mortality [103], and these same benefits have been seen in the coinfected population [104]. Several studies have shown, however, that HCC can develop in individuals with cirrhosis even after cure of chronic HCV [33, 105]. Guidelines for the management of coinfected patients after achieving SVR have been summarized by Zator and Chung [106]. Studies are ongoing to determine factors that may predict regression of inflammation and/or fibrosis in mono- and coinfectedparity of response to antiviral patients who achieve SVR [107•, 108•].

In patients with chronic HBV, HBV DNA level has been show to increase after achieving SVR, and this population should be checked for HBV viral breakthrough/flare. In the past, interferon containing regimens had activity against both HBV and HCV, but current DAAs have unmasked this potential for HBV flare [109••]. We test HBV serologies in all patients prior to DAA-based therapy. In patients with prior HBV exposure (HBV core IgG positive) who experience elevated aminotransferases during DAA therapy, we will assess HBV DNA and consider anti-HBV viral therapy accordingly.

Cytomegalovirus Coinfection and Accelerated Aging

Accumulation of differentiated $CD8^+$ T-cells, strongly enhanced in CMV-infected individuals, has been linked to aging and cell senescence. Long-term cART, while suppressing HIV, has been shown to exacerbate CMV infection. Parrinello and colleagues have shown that increased CMV IgG levels are associated with carotid artery stiffness in HIV+ [110]. This association was observed in treated and untreated HIV+ groups and was specific to CMV. However, the authors found carotid artery lesions only among HIV+ on cART with undetectable viral load, after adjustment for age, race, and smoking history. Inflammation and T-cell activation contribute to atherosclerosis in the general population. HIV+ on cART have a higher number of CMV specific T cells possibly related to a dysfunctional response to normal levels of subclinical CMV replication [111]. A more recent study by Rector and colleagues has shown higher glycosylated hemoglobin levels and poorer lipid profiles in CMV+ individuals without HIV. Glycemic control may, in turn, contribute to

immunosenescence by amplifying the effects of CMV on T cell differentiation [112•].

The accumulation of memory CD8 T lymphocytes is seen in both HIV+ and in immunosenescence. Chronic antigenic stimulation by persistent CMV infection is a hallmark of HIV and aging. Effros reviewed the effects of CMV in aging and HIV infection, concluding "Since nearly all HIV-infected persons are also infected with CMV, it seems likely that this persistent infection, probably acquired prior to HIV, plays a substantial role in the accelerated immunosenescence. Clinically, the development of such geriatric syndromes as frailty, and multimorbidity are hastened in chronic HIV infection, and many age-associated pathologies, such as cardiovascular disease and bone loss may be accentuated, suggesting that HIV and CMV may confer 'double indemnity'."

We can learn about common diseases that affect the general population from the multifactorial aging we see in the HIV+ population. Studying the effects of immune activation and dysfunction in HIV+ has already given us significant insight into age-related illnesses, such as diabetes, cardiovascular disease, frailty, and neurocognitive impairment, all more prevalent in HIV+ of all ages than those without infection [113••].

Conclusion

The natural history of HIV disease is changing and we must, as a scientific community, carefully annotate these changes in all areas of research, from population health to the bench. While we can suppress virus with cART and achieve better health and longevity, we must strive to better understand the effects of cART on immune activation and dysregulation. Coinfection and aging are also dynamic phenomena that have their own changing natural histories that intersect in complex and overlapping ways with HIV infection. We must embrace the complexity of these issues with careful study design in which we are able to assess not only the characteristics of specific populations, but the significant genetic, epigenetic, and environmental factors that contribute to disease. This type of phenotype-genotype annotation requires large, multicenter, collaborative, and translational teams. The insights we gain will be broadly applicable to cancer, liver disease, and the common comorbidities of aging.

Compliance with Ethical Standards

Conflict of Interest Tamar H. Taddei reports grants from Bayer Healthcare Pharmaceuticals and consulting fees from Onyx (Amgen) Pharmaceuticals.

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