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Editorial

Hepatocellular carcinoma in HIV-infected patients comes of age: The convergence of epidemiology and treatment effectiveness ☆

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The early 21st century has witnessed the maturation of HIV, HBV and HCV epidemics with respect to disease recognition, understanding and medical treatment. Most notably, the availability of safe, potent antiretroviral therapy (ART) in settings with adequate resources has transformed HIV infection into a chronic disease that, for many infected patients, may not substantially limit life expectancy [1,2]. Consequently, chronic medical conditions such as diabetes mellitus, hypertension, coronary artery disease, viral hepatitis-related liver disease and malignancy have emerged as major causes of morbidity and mortality in HIV-infected patients; many of whom are over the age of 50 [3–7]. Indeed, Weber et al., observed that the most frequent causes of death among more than 23,400 HIV-infected patients receiving medical care in Europe were: HIV/AIDS (31% of observed deaths), liver disease (15%), cardiovascular disease (11%) and malignancy (9%) [6]. Of course, the observation that liver disease is an important cause of death in HIV-infected persons in the era of ART is not unexpected in light of the relatively high prevalence of chronic HBV (~6–10%) and HCV (~33%) co-infection, accelerated HCV disease progression in the setting of HIV, and long duration of HIV and HCV disease in many patients [8]. Until recently, hepatic decompensation has been the major etiology of liver death in persons co-infected with viral hepatitis and HIV [9,10]. Indeed, in a meta-analysis derived largely from studies of men with hemophilia, Graham et al., found that HIV-infected persons were ~2- and 6-fold more prone to develop cirrhosis and hepatic decompensation compared to persons without HIV [9]. Although clearly linked to chronic HBV and HCV infection in other populations, hepatocellular carcinoma (HCC) was simply not frequently observed in early HIV cohort studies, many of which were conducted prior to the introduction of potent ART. In the second decade of highly effective ART, several studies suggest that HCC may be increasing in HIV-infected persons, particularly in those co-infected with hepatitis C [11–16]. In this issue of the *Journal*, the study by Salmon et al., [17] reports that in France, the proportion of liver-related deaths due to hepatocellular carcinoma increased from 15% in 2000 to 25% in 2005 with underlying HCV infection in the majority (HCV/HIV, 69% and HCV/HBV/HIV, 11%) of deaths due to HCC whereas HBV was the sole risk factor in only 17% of cases.

Why is HCC emerging in HIV/HCV co-infected patients? The explanation is likely due to multiple factors: First, in the era prior to potent HIV treatment, HIV/HCV co-infected patients did not survive long enough to permit the clinical presentation of HCC [18]. In these early studies, the cause of death in co-infected patients was often due to AIDS, opportunistic infections (OIs), or hepatic decompensation and the incidence of non-AIDS related malignancy (e.g., lung and liver cancer) was relatively low. Quite simply, persons who died of AIDS or AIDS-related illnesses could not develop hepatocellular carcinoma. Second, HIV

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disease may increase the likelihood of developing HCC. In the United States (1992–2001), Giordano et al., reported that the development of HCC was 5-fold higher in HIV/HCV-infected patients compared to those with HCV alone [19]. Similarly, in a prospective observational cohort (1992–2003), Patel et al., observed that this incidence of liver cancer was 7.7-fold higher in HIV-infected persons compared to the US general population [5]. Third, treatment with potent ART may be associated with decreased risk of hepatic decompensation in co-infected patients with cirrhosis [20,21]. This effect has been most noticeable in the setting of HBV-related cirrhosis in which suppression of HBV replication by commonly prescribed antiretroviral agents may delay or prevent liver failure [22–24]. While more controversial and less apparent, potent ART may also reduce the likelihood of liver failure due to HCV disease. In a retrospective cohort, Pineda et al., observed that liver failure was significantly more common among HCV co-infected persons who were not taking effective ART [20]. Similarly, in the United States Solid Organ Multi-Site Transplant Study, death while waiting for liver transplant was associated with higher baseline Model for End-stage Liver Disease (MELD) score and detectable baseline HIV RNA, suggesting that despite concerns about drug-induced liver injury, ART may delay death in persons with advanced liver disease [25]. Fourth, increased awareness of liver disease among HIV clinicians may have led to improved medical management of HIV-infected patients with advanced liver disease to prevent fatal complications of cirrhosis. While data are lacking, the greater implementation of measures to prevent and/or treat spontaneous bacterial peritonitis, bleeding esophageal varicies and hepatic encephalopathy should prevent or delay death due to hepatic failure. Fifth, HCV treatment with interferon in combination with ribavirin in HIV-infected patients has been associated with only modest rates of sustained virologic response (standard interferon/ribavirin, ~12% and peginterferon/ribavirin, ~40%) and, in many settings, very limited rates of HCV treatment uptake [26,27]. For example, in one urban HIV clinic, less than one in three of HCV co-infected patients receiving HIV care had been referred to an on-site clinic for HCV treatment [28]. In the current study by Salmon and co-workers more than 50% of the persons who died of liver disease had taken HCV treatment but more than 98% had failed to eradicate HCV infection. Thus, from an individual patient and public health perspective, the overall effectiveness of HCV treatment on the natural history of HCV disease in HIV co-infection has been relatively small. Taken together, these factors indicate that the emergence of HCC in HIV/HCV infected patients in the second decade of potent ART was predictable.

The observations by Salmon and colleagues of HCC in French patients are likely a harbinger of an emerging problem for persons living with HIV/HCV co-infection regions with access to potent ART. Further, the study raises an important question: what steps are needed to confront the challenge of HCC in HCV/HIV infected patients? The answer to this question will likely involve the combination of multiple approaches:

(1) **Treatment of HIV disease.**

While some studies suggest that ART may slow the progression of HCV disease, recent analysis by Thein et al., suggest that potent ART will not fully correct the negative impact of HIV infection of the risk of HCV-related cirrhosis [29]. Further, Salmon et al., reported that HCC occurred in many patients despite the use of effective ART for more than a median of 7 years. Thus, antiretroviral therapy is unlikely to modify the risk of HCC in HCV-infected patients in whom the risk of cancer is driven by HCV-related cirrhosis.

(2) **Treatment of HCV disease.**

While not effective for all co-infected patients, the treatment of HCV infection in HIV-infected patients at risk for cirrhosis is strongly recommended [30,31]. Nonetheless, in some settings, HCV treatment rates remain relatively low (compared to HCV mono-infected patients). Measures to better implement consensus HCV treatment recommendations in HIV-infected patients are needed. While increased delivery of HCV treatment could be expected to benefit individual patients, current therapy are likely to have only modest effects on the incidence of HCC in the short term. While HCV protease and/or polymerase inhibitors are expected to increase SVR rates in co-infected patients, studies of these agents have not been conducted and significant questions must be answered regarding drug–drug interactions, tolerability, and HCV drug resistance [32,33]. In addition, these drugs will be added to existing therapy with peginterferon and ribavirin which may serve to limit their use in HIV-infected patients with comorbid psychiatric disease and anemia.

(3) **Treatment of hepatocellular carcinoma.**

If HIV and HCV treatments are unlikely to stem the development of HCC in the short-term, interventions must focus on improving early diagnosis and management of HCC in HIV-infected persons. While definitive evidence of benefit is lacking, the American Association for the Study of Liver Disease and European Association for the Study of the Liver recommend routine screening of persons with HCV or HBV-related cirrhosis with serial liver imaging and, in some studies, serum α-fetoprotein levels [33]. Screening of at risk HIV-infected patients (i.e. those with cirrhosis) for hepatocellular

carcinoma has not been systematically evaluated and practice patterns vary widely across clinical care settings. Despite the paucity of data, the rationale for routine screening is to facilitate the diagnosis of HCC at earlier stages, permitting more effective medical and surgical interventions. As such, clinicians caring for HIV/HCV infected patients with advanced fibrosis (bridging fibrosis or cirrhosis) must incorporate HCC screening as part of their routine medical practice. If HCC is identified, recent advances in the treatment of hepatocellular carcinoma mandate prompt referral for consideration of treatment with systemic chemotherapy, transarterial chemoembolization (TACE), radiofrequency thermal ablation (RFTA), surgical resection and/or liver transplantation. Interestingly, in a retrospective study of 63 HIV-infected patients with HCC, Brau et al., reported that the receipt of HCC therapy known to be effective in patients without HIV was independently associated with increased survival in HIV-infected patients [12]. While this retrospective analysis is promising, data on the safety and effectiveness of these and other interventions in HIV-infected persons is limited and carefully designed studies must be conducted. In several settings in the US and Europe, ongoing studies of liver transplantation in HIV-infected patients are expected to provide some data on transplant outcomes of co-infected persons with HCC [34,35]. Additional prospective studies are needed to define the role of systemic chemotherapy including sorafenib and loco-regional therapy including [36] ablation and TACE. Existing clinical research networks focused on HIV disease should take the lead on the design and implementation of such studies.

Thus, as the HIV epidemic enters the second decade of potent ART, patients living with HIV disease will undoubtedly continue to experience problems related to concurrent chronic conditions, including viral hepatitis. Coupled with the recent increase of HCC observed in HCV-infected patients without HIV disease, the observation by Salmon et al., that HCC is emerging as an important problem in HIV/HCV infected patients is not unexpected. Nonetheless, these data should encourage heightened clinical vigilance for hepatocellular carcinoma in this population and should stimulate well-designed, prospective research on the pathogenesis and treatment of HCC.

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