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Is HIV Still a Special Population for the Treatment of Hepatitis C?

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Hepatitis C virus (HCV) is a blood-borne virus that infects persons living with HIV (PLWH) more frequently than the general population [1]. This is due to shared risk factors for transmission, mainly percutaneous exposure to blood or blood products contaminated with HCV and/or sexual transmission particularly among HIV-infected men who have sex with men [2]. Roughly 4.5 million of PLWH are co-infected with HCV [1]. Until recently co-infected individuals have been considered a special population because they progressed faster to end stage liver disease and responded less to interferon-based therapies than HCV-monoinfected persons [3,4]. Interferon relies on activating individuals' immune response to clear HCV, and immunity is already impaired in PLWH. Since less than 5% of HIV-infected individuals with known HCV infection were treated in the interferon era [4,5], not surprisingly HCV has become the leading cause of liver-related mortality among otherwise well controlled PLWH on antiretroviral therapy [6].

In the new era of direct-acting antivirals (DAA) against HCV, clinical trials have shown consistently that PLWH can achieve sustained viral response (SVR) rates in excess of 90%, similar to patients without HIV co-infection [7]. Although management of drug-drug interactions (DDI) between DAA and antiretroviral medications remains an important caveat, several online resources help to manage DDI and ease clinicians work when considering HCV treatment initiation in this population. Does this mean that we need to stop considering PLWH co-infected with HCV as a special population for the treatment of hepatitis C? We believe that the answer is No.

To place in perspective the promising SVR rates obtained in HCV clinical trials that offer the potential of curing most PLWH co-infected with HCV, we propose to conceptualize SVR as the net result of an equation that depends on three key clinical variables: i) intrinsic antiviral effect, ii) drug exposure and concurrent comorbidities, and iii) ongoing barriers to

care (Figure 1). In most clinical trials, SVR rates were the direct reflection of the potent DAA antiviral efficacy because the other factors of the equation were part of their exclusion criteria and therefore ultimately did not impact on SVR [8]. In other words, a careful selection of PLWH was made in HCV registration clinical trials to demonstrate that HIV was not a negative predictor of DAA response.

In real life, most PLWH co-infected with HCV in Western countries have an extensive HIV medication history and frequent comorbid conditions [4]. Emerging data from real-world HIV-HCV cohorts demonstrate that antiretroviral changes prior to HCV therapy are common, above 40% of PLWH who initiate HCV therapy in our experience [9]. Moreover, up to 30% of them were antiretroviral-experienced patients with prior HIV drug resistance, complicating drug choices and avoidance of harmful DDI [9]. Increasing concerns on DDI and polypharmacy exist due to the higher prevalence of concurrent comorbidities in PLWH compared to the general population [4]. The presence of these comorbidities not only increases the number of medications and potential risk for DDI, but also could restrict DAA options in PLWH due to additional concerns, such as recently highlighted using sofosbuvir along with amiodarone [10]. On the other hand, the higher prevalence of hepatitis B or delta in PLWH might account for more frequent HBV reactivation episodes and force premature DAA discontinuation [11].

PLWH co-infected with HCV have a high prevalence of ongoing barriers to care, such as active drug/alcohol use, neuropsychiatric disease and/or unstable housing. In fact, the presence of ongoing barriers to care was the main reason for not initiating HCV therapy in PLWH in the interferon era [4]. From a practical stand point, successful HCV treatment of patients with ongoing barriers to care can be accomplished, but requires a dedicated multidisciplinary team to support them [12]. In particular, monitoring DAA adherence and minimizing risk behaviors are the most crucial. A worrisome scenario would be illustrated by inadequate DAA adherence along with ongoing risk behaviors, such as active injection drug use and/or persistent high-risk sexual practices. In all likelihood, this scenario can increase the chances of HCV re-infection [13], or treatment failure, selection, and transmission of resistance-associated variants (RAVs) [14]. Periodic surveillance of DAA resistance would be advisable in these populations, especially to NS5A inhibitors for which RAVs do not vanish and persist over time, compromising most current DAA combinations [15].

In a recent real-world study, 363 chronic hepatitis C patients were examined and it was found that HIV was an independent predictor for lack of HCV treatment response [16]. Whether this observation was due to an individual factor (e.g., greater viral load, more frequent genotype 3, etc.) [17] or synergistic effect of several of the aforementioned parameters in our proposed equation other than viral efficacy remains unclear.

Enthusiasm unabated, nowadays using DAA we can cure HCV in most PLWH. Although they will respond equally well as the general population in terms of HCV antiviral efficacy, special efforts must be devoted to avoid negative DDI, manage properly coexistent comorbidities and address ongoing barriers to care. The latter factors can affect drug adherence, create toxicity and affect the ultimate goal of achieving SVR. Only with a deeper

understanding of the issues surrounding what makes PLWH co-infected with HCV a special population, can we unite efforts to scale-up DAA therapy in an era where HCV could be an eradicable disease, indeed across different geographical areas and health care systems.

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Figure 1. The equation for hepatitis C therapy success