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EDITORIAL

Hepatitis C virus eradication in people living with human immunodeficiency virus: Where are we now?

Anna Maria Spera, Pasquale Pagliano, Valeria Conti

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Abstract

Hepatitis C virus (HCV)/human immunodeficiency virus (HIV) co-infection still involves 2.3 million patients worldwide of the estimated 37.7 million living with HIV, according to World Health Organization. People living with HIV (PLWH) are six times greater affected by HCV, compared to HIV negative ones; the greater prevalence is encountered among people who inject drugs and men who have sex with men: the risk of HCV transmission through sexual contact in this setting can be increased by HIV infection. These patients experience a high rate of chronic hepatitis, which if left untreated progresses to end-stage liver disease and hepato-cellular carcinoma (HCC) HIV infection increases the risk of mother to child vertical transmission of HCV. No vaccination against both infections is still available. There is an interplay between HIV and HCV infections. Treatment of HCV is nowadays based on direct acting antivirals (DAAs), HCV treatment plays a key role in limiting the progression of liver disease and reducing the risk of HCC development in mono- and coinfected individuals, especially when used at an early stage of fibrosis, reducing liver disease mortality and morbidity. Since the sustained virological response at week 12 rates were observed in PLWH after HCV eradication, the AASLD has revised its simplified HCV treatment algorithm to also include individuals living with HIV. HCV eradication can determine dyslipidemia, since HCV promotes changes in serum lipid profiles and may influence lipid metabolism. In addition to these apparent detrimental effects on the lipid profile, the efficacy of DAA in HCV/HIV patients needs to be considered in light of its effects on glucose metabolism mediated by improvements in liver function. The aim of the present editorial is to describe the advancement in HCV treatment among PLWH.

Key Words: Hepatitis; People living with human immunodeficiency virus; Direct acting antivirals; Highly active antiretroviral therapy; Co-infection

Core Tip: Considering the quite high prevalence of hepatitis C virus (HCV) co-infection in people living with human immunodeficiency virus (PLWH), along with the interplay of HCV and human immunodeficiency virus infections, the usefulness of direct acting antivirals (DAAs) therapy regimen for the cure of HCV in this context appears crucial. However, apart from several known drug-drug interactions between highly active antiretroviral therapy (HAART) and DAAs, the metabolic impact of HCV eradication in terms of worsening of lipid profile as well as the improvement of glucose metabolism must be taken into account. The treatment of HCV infection in PLWH under HAART represents a challenge as well as a great opportunity for clinicians and deserves attention.

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INTRODUCTION

Hepatitis C virus (HCV) infection is a major concern for physicians dealing with human immunodeficiency virus (HIV)-positive patients. According to a World Health Organization report, 2.3 million patients worldwide, of which 37.7 million are estimated to be living with HIV, are coinfected with HCV. These patients experience a high rate of chronic hepatitis, which if left untreated progresses to end-stage liver disease and hepatocellular carcinoma (HCC)[1]. HCV and HIV share the same routes of transmission, and HCV infection is estimated to be six times more frequent among people living with HIV (PLWH) than among HIV-negative individuals. HCV/HIV coinfection is most common in low-income countries, and the highest prevalence is found among people who inject drugs and men who have sex with men[2,3]. Moreover, HIV infection increases the risk of vertical transmission of HCV from mother to child[4].

The outcome of HCV-related liver disease is influenced by the immune deficit caused by HIV, which can lead to a rapid progression to liver cirrhosis and HCC[5]. HIV can affect the progression of HCV-related liver disease through both direct and indirect effects. Direct effects involve the liver at different levels: (1) HIV-mediated apoptosis of hepatocytes[6] and oxidative stress[7]; (2) inflammation and fibrinogenesis of hepatic stellate cells[8]; and (3) activation of Kupffer cells [9]. Indirect effects are related to the functional alteration of the HCV-specific immune response caused by HIV, which favors HCV replication[10], and to highly active antiretroviral therapy (HAART), which can lead to liver fibrosis[11] by increasing intracellular lipid accumulation because of insulin resistance related to treatment[12].

As a result of these interactions, HCV infection can worsen the morbidity and mortality of coinfected PLWH and delay immune reconstitution after HAART[13]. Moreover, DAA treatment for HCV can mobilize the HIV viral reservoir from tissues[14].

TREATMENT OF HCV

Treatment of HCV infection in HIV-coinfected patients became a major concern after the advent of HAART, as it allowed considerable improvement in terms of the survival of PLWH, which ultimately revealed the impact of HCV on HIV-positive patients in terms of survival. The first approved treatment for HCV infection in PLWH was PEG- IFN-alpha, and the cure rate was further increased after ribavirin was added to the treatment protocol[15]. The absolute number of CD4+ lymphocytes, current HAART and rs12979860 polymorphism of the gene encoding the IL28B receptor have been shown to predict the response to IFN-based treatments among HCV/HIV-coinfected subjects with genotypes 1-4[16]. In addition, Mandorfer *et al*[17] hypothesized that the serum 25OH-D3 Level is a marker of the response to IFN among coinfected patients.

Further advances could be achieved by adding the HCV protease inhibitors (PIs) boceprevir or telaprevir to PEG-IFN-ribavirin regimens, as demonstrated in multicenter randomized, double-blind placebo-controlled trials. This treatment regimen conferred a better response rate than previously reported, but a considerable number of HCV/HIV patients could not complete the treatment due to side effects or lack of viral clearance after 2 or 4 wk of treatment. Similar findings were reported when the same treatments were proposed for HCV monoinfected patients[18].

These antiviral protocols used to treat HCV/HIV-coinfected patients have a low cure rate and cannot be applied to all PLWH due to the many drug-drug interactions (DDIs) with the available anti-HIV agents. For example, boceprevir [a strong inhibitor of CYP3A4/5 and a potential inhibitor of P-glycoprotein (P-gp)] interferes with efavirenz and all ritonavir-enhanced HIV PIs; in contrast, telaprevir (a substrate and inhibitor of CYP3A and P-gp) interferes with some

RTV-enhanced PIs[19].

Since 2014, the use of direct antiviral agents (DAAs) has represented a milestone for HCV infection treatment in both coinfected and monoinfected patients[20].

The usefulness of treating HCV coinfection in PLWH arose from a phase 4, open-label, single-arm trial, the MINMON study, which was based on the comparison of hepatitis C treatment among HIV-positive and HIV-negative individuals between October 2018 and July 2019[21].

Since the sustained virological response (SVR) at week 12 (SVR12) rates were observed in those populations after HCV eradication, the AASLD has revised its simplified HCV treatment algorithm to also include individuals living with HIV. DAA-based treatments can be administered for a shorter duration than PEG-IFN/ribavirin plus boceprevir or telaprevir-based regimens and have a better virological response rate and a lower frequency of side effects requiring drug withdrawal. Currently, simplified HCV treatment for HbsAg-negative naïve adults without cirrhosis is based on the pangenotypic NS3/4A protease inhibitor glecaprevir co-formulated with the pangenotypic HCV NS5A inhibitor pibrentasvir for 8 wk (phase 3, multicenter EXPEDITION-2 study)[22]; instead, a 12-wk treatment for treatment-experienced or naïve patients aged > 3 years with any stage of liver fibrosis is based on the pangenotypic HCV NS5B polymerase inhibitor sofosbuvir (SOF) co-formulated with the pangenotypic HCV NS5A inhibitor velpatasvir (VEL)[23]. Treatment based on SOF/VEL plus the NS3/4A reversible protease inhibitor voxilaprevir may be evaluated in cases of treatment failure[24].

The introduction of DAAs into clinical practice represents a revolution in the care of patients with HCV/HIV coinfection, but there are some concerns about several DDIs between the antivirals active against HCV and those used for HAART, particularly if we consider regimens including HIV protease inhibitors. This event is not surprising, as HIV protease inhibitors can lead to important adverse events in many clinical settings when other antiviral treatments are planned[25].

In particular, the glecaprevir/pibrentasvir regimen is contraindicated with HIV protease inhibitor-based regimens, including atazanavir, darunavir, lopinavir, saquinavir, and tipranavir (notably, some of them are currently largely used). In these cases, coadministration may affect the risk of alanine transaminase elevation due to a threatened increase in plasma levels of glecaprevir or pibrentasvir caused by inhibition of the organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1/3)[26].

In addition to interactions occurring in those receiving HIV protease inhibitors, other relevant DDIs have been described in HCV/HIV patients receiving DAAs. In fact, caution should be exercised when SOF/VEL is used with tenofovir disoproxil fumarate (TDF) due to possible inhibition of the P-gp transporter-mediated efflux of TDF caused by velpatasvir, which increases the risk of TDF toxicity.

Moreover, it should be noted that in particular settings, HCV treatment must be delayed despite decreasing the risk of HCV transmission due to the toxicity of DAAs, as we observed in pregnant/Lactating women[27].

Although a very high cure rate for HCV infection can be obtained in PLWH, we should consider that the percentage of coinfected patients experiencing treatment failure can be greater. In fact, a prospective multicohort study including 908 Spanish patients, 46.9% of whom were HCV/HIV coinfected and treated with DAA-based therapy, highlighted a cure rate approaching 86% for HCV/HIV patients, as opposed to the 95% cure rate obtained among HIV-negative patients. In this setting, relapse after the DAA-based regimen was observed in 10/231 (4.4%) HIV/HCV-coinfected subjects compared to 3/208 (1.4%) HCV-monoinfected subjects. The authors of the study highlighted that the absence of HIV coinfection (adjusted odds ratio: 3.367; 95% confidence interval: 1.15-9.854; $P = 0.027$) was independently associated with a SVR12 by multivariate analysis adjusted for age, sex, transmission route, body mass index, HCV genotype, and cirrhosis. This finding clearly demonstrates the effect of HIV-related immune compromise on the outcome of HCV treatment[28].

In another study, Sikavi *et al*[29] compared efficacy data from clinical trials to effectiveness data from real-world observational studies in HIV/HCV patients. They showed that the SVR among HCV/HIV coinfected patients treated with DAA regimens is high in the real-world setting and is similar to the SVR of patients reported in clinical trials.

GOAL OF DAA-BASED THERAPY

HCV treatment plays a key role in limiting the progression of liver disease and reducing the risk of HCC development in mono- and coinfected individuals, especially when used at an early stage of fibrosis, reducing liver disease mortality and morbidity[30,31].

In HIV/HCV patients, several factors, including metabolic abnormalities and gut dysbiosis, which may lead to hepatic steatosis and accelerate liver damage and the development of HCC, should be evaluated in patients receiving DAA therapy[32].

Available data suggest that the HIV reservoir burden is greater in HIV/HCV-coinfected individuals than in HIV-monoinfected individuals, and several studies have revealed an increase in integrated HIV DNA after DAA treatment in coinfected patients with low-level HIV viremia at baseline[33]. In fact, some investigations have demonstrated that after successful treatment with DAA, HIV reservoirs are activated by the lymph nodes, liver and other organs in the endothelial reticle, leading to an increase in the level of HIV DNA in peripheral blood cells[34]. The exact impact of this phenomenon is not fully understood and should receive further investigation, but we can recommend careful evaluation of HIV replication in the follow-up period after HCV treatment completion.

METABOLIC OUTCOMES OF HAART/DAA-BASED THERAPY

It should be mentioned that HCV promotes changes in serum lipid profiles and may influence lipid metabolism, further increasing cardiometabolic risk in coinfected patients. This phenomenon should be considered in light of the metabolic impact of HAART.

HCV eradication in monoinfected individuals also worsens the lipid profile, leading to additional cardiovascular risk factors due to increased total blood cholesterol and weight gain. This effect can be attributed to the statin-like effect of HCV and to the improvement in liver function, which boostscholesterol synthesis. Trifan *et al*[35] conducted a prospective study involving 132 HCV-infected patients with different stages of liver damage. They found an increase in BMI and the mean total cholesterol value at follow-up compared to baseline when HCV eradication could be obtained [$P = 0.014$].

Estefan *et al*[36] conducted another observational, cross-sectional study of 97 HCV-infected, overweight, hypertensive, dyslipidemic and prediabetic or diabetic patients. They found a significant increase [$P < 0.001$] in total cholesterol and LDL levels and a borderline reduction in blood glucose, insulin, glycated hemoglobin, and homeostasis model assessment (HOMA)-IR levels after DAA treatment.

In addition to these apparent detrimental effects on the lipid profile, the efficacy of DAA in HCV/HIV patients needs to be considered in light of its effects on glucose metabolism mediated by improvements in liver function. Shiffman *et al* [37] examined the impact of HCV on glucose metabolism and suggested that successful infection treatment reduces the risk of developing insulin resistance, type 2 diabetes mellitus, chronic kidney disease and stroke, providing significant public health benefits. Morales *et al*[38] conducted a retrospective analysis of HCV-positive patients with altered HbA1c levels treated with SOF regimens from January 2014 to March 2015 and demonstrated a significant reduction ($P < 0.005$) in HbA1c after HCV eradication. Sparvoli *et al*[39] compared glucose metabolism by HOMA among 273 HCV patients treated with DAAs from March 2018 to December 2019 and reported a significant reduction in HbA1c among prediabetic patients ($P = 0.006$).

CONCLUSION

In conclusion, HCV eradication in HIV-coinfected patients has a favorable impact on the progression to liver cirrhosis and HCC. This impact should be considered when examining the effects on glucose metabolism due to improvements in terms of liver function. However, these positive effects should be considered in light of the changes in the lipid profile, which warrant appropriate monitoring and additional treatment strategies, including statins and antiplatelet drugs, to avoid further increases in cardiovascular risk constitutively associated with both HIV infection and HAART.

FOOTNOTES

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