

# Management Of Patients With Hepatitis B Virus Reactivation Post–DAA Treatment Of Chronic Hepatitis C Virus Infection In HCV–HBV Coinfected Patients With Pretreatment HBeAg Seroconversion And Early Degree Of Hepatic Fibrosis

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**Background and aim:** Hepatitis C virus (HCV)–HBV coinfection is a significant health problem with rapid progression of liver disease without precise diagnosis and treatment. We aimed in this study to identify if there were any role of HBV antiviral therapy in patients with HBV reactivation after direct-acting antiviral therapy in HCV–HBV coinfecting patients.

**Methods:** A prospective random study was carried out on 140 patients presenting with chronic HCV and chronic HBV coinfection. All patients had pretreatment HBeAg seroconversion, HBV DNA <2,000 IU/mL, normal liver enzymes, and F0/F1 hepatic fibrosis. They treated with sofosbuvir 400 mg and daklatasvir 60 mg once daily for 3 months. All patients underwent pretreatment hepatic fibrosis assessment using Fibro Scan and laboratory investigations: platelet count, liver-function tests, quantitative HCV PCR, HBsAg, HBc IgG, HBeAg, and HBeAb. All patients were followed up at 1, 3, 6, and 12 months from the start of HCV therapy.

**Results:** The study enrolled 140 HCV–HBV coinfecting patients: 55% were F0 and the rest F1. All our patients had negative HCV PCR at 1 month posttreatment and had achieved sustained virologic response with negative HCV PCR 3 months after treatment end. Four patients showed HBV reactivation with raised HBV DNA PCR and liver enzymes. Their mean age was 23.7±2.7 years, and three were male. Regarding patients with HBV reactivation, at 12 months posttreatment they showed significant decreases in liver enzymes, bilirubin, and INR, with increased platelet count ( $P=0.001$ ), each with undetectable HBV PCR ( $P=0.001$ ).

**Conclusion:** HBV–HCV coinfecting patients with no/mild hepatic fibrosis, HBeAg seroconversion, and HBV DNA <2,000 IU/mL can complete direct-acting antiviral therapy without HBV antiviral treatment with close monitoring.

**Keywords:** HBV, HCV, PCR, DAAs

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## Introduction

Hepatitis B virus (HBV) infection is still a global health affair. Patients who progress to chronic HBV can early develop liver cirrhosis and hepatocellular carcinoma, with an accession risk of morbidity and mortality.<sup>1</sup> HBV and HCV

infections share the same transmission routes, so the presence of HBV coinfection in patients with HCV infection is frequent.<sup>2</sup> The presence of HBV surface antigens in patient blood is known as overt HBV infection. However, in the absence of an HBsAg test, detection of HBV DNA is recognized as occult HBV infection, and is commonly found in patients with chronic HCV infection.<sup>3</sup>

Coinfection with HBV and HCV is common in Southeast Asia and the Mediterranean.<sup>4</sup> HBV–HCV coinfection is associated with higher incidence of cirrhosis, hepatic decompensation, and development of primary liver malignancy (hepatocellular carcinoma) compared with monoinfected individuals.<sup>5</sup> The true prevalence of HBV–HCV coinfection is unknown.<sup>6</sup> HBsAg-positive patients have been excluded from clinical trials during treatment of patients with chronic HCV with direct-acting antivirals (DAAs).<sup>7</sup> This was confirmed by a different study wherein interaction between HBV and HCV in coinfecting patients led to suppression of HBV replication.<sup>8,9</sup> However, severe cases of chronic HBV reactivation after HCV clearance have been reported after DAA therapy, which led to US Food and Drug Administration concern about the risk of HBV reactivation with DAA therapy.<sup>10</sup>

## Aim

The aim of this work was to identify if there was any role of HBV antiviral therapy following DAA treatment of chronic HCV infection in HBV reactivation in patients with pretreatment HBeAg seroconversion, HBV DNA <2,000 IU/mL, normal liver enzymes, and F0/F1 hepatic fibrosis.

## Methods

This prospective randomized study was carried out on 140 patients presenting with chronic HCV–HBV coinfection who had been referred to the outpatient clinic of the Tropical Medicine and Gastroenterology Department of Qena University Hospital. The study period was from August 1, 2016 to January 1, 2019. HBV PCR  $\leq$ 2,000 IU/mL, normal liver enzymes, HBeAg seroconversion with formation of HBeAb before treatment, and F0/F1 hepatic fibrosis were the inclusion criteria. Patients with worse than F1 hepatic fibrosis, previous HBV antiviral treatment, absence of HBeAg seroconversion, had failed previous HCV therapy, and malignancy anywhere in the body, including hepatocellular carcinoma and laboratory parameters of hepatic decompensation, pregnancy,

autoimmune disease, and uncontrolled diabetes mellitus were excluded from the study.

All included patients were treated with sofosbuvir 400 mg and daklatasvir 60 mg once daily for 3 months following the Egyptian protocol for treatment of chronic HCV infection, which is based on the European Association for the Study of the Liver guidelines for treatment of HCV infection.<sup>11</sup> All patients underwent pretreatment complete history taking, full clinical examination, and laboratory investigations, including liver-function tests, platelet count, prothrombin time, prothrombin concentration, and INR. Quantitate HCV PCR, HBsAg, HBc IgG, HBeAg and HBeAb were also assessed. Also, all patients underwent pretreatment hepatic fibrosis assessment using a FibroScan FS502. Hepatic scans were performed after overnight fasting. Liver stiffness correlate directly with wave velocity. FibroScan results were correlated with the METAVIR histological staging system. Cutoff values in our study were 5.4–6.9 kPa.<sup>12</sup> All patients were followed up at 1 month, 3 months (end of HCV treatment), 6 months (to confirm HCV sustained virologic response), and 12 months (to confirm absence of HBV reactivation) from the start of HCV therapy.

## Blood Sampling

Venous blood (8 mL) was collected from each patient under aseptic precautions and divided in four tubes: two tubes containing EDTA, one for platelet count used directly and the other for HBV DNA, HBc IgG, HBeAg, and HBeAb centrifuged, separated in sterile tubes, and frozen at  $-20^{\circ}\text{C}$  until assay; a plain glass tube for liver-function tests, after clotting the tube being centrifuged at 3,000 rpm for 5 minutes at room temperature and then serum was separated to be used for estimation of liver function (including liver enzymes, albumin, and bilirubin); and a sodium citrate-containing tube for prothrombin time, prothrombin concentration, and INR.

## Laboratory Tests

Venous blood (5 mL) was obtained from each subject in a plain tube, centrifuged, and then the serum separated for laboratory tests. Platelet counts were done with a Celtak hematology analyzer (Nihon Kohden). Liver-function tests (total and direct bilirubin, serum albumin, AST, and ALT) were done with a BT 1500 fully automated chemistry analyzer (Biotechnica). Prothrombin time, concentration, and INR were assessed using Thromborel S kits (Siemens) using a BE coagulator. HBV DNA, HBc IgG,

HBeAg, and HBeAb were assessed with a StepOnePlus real-time PCR system (Thermo Fisher Scientific) using TaqMan PCR master mix (Thermo Fisher Scientific) after DNA extraction with a Qiagen kit and according to the manufacturer's pamphlet. HCV PCR and HBsAg were measured with a MiniVidas fully automated immunoassay system (Biomérieux).

## Statistical Analysis

Data were analyzed using SPSS version 15.0. Quantitative data are expressed as means  $\pm$  SD. Qualitative data are expressed as frequencies and percentages. Independent-sample *t*-tests were used when comparing two means,  $\chi^2$  when comparing nonparametric data, and one-way ANOVA when comparing more than two means. Significance was established at  $P < 0.05$ .

## Ethical Considerations

The study protocol was approved by the Medical Ethics Committee of South Valley University, and the study was performed in accordance with clinical ethics guidelines, the Declaration of Helsinki, and rules of good clinical practice. All patients provided informed consent for participation in the study. No specific medical intervention was conducted specifically.

## Results

The study enrolled 140 patients coinfecting with HCV–HBV. All patients had HBV PCR  $\leq 2,000$  IU/mL, normal pretreatment liver enzymes, and showed HBeAg seroconversion with development of HBeAb. In sum, 77 (55%) were F0 and 63 (45%) F1, mean age was 32.4 $\pm$ 8.02 years, and 96 (68.6%) were male and 44 (31.4%) female. Four patients (2.86%, three male, mean age 23.7 $\pm$ 2.7 years) showed HBV reactivation in the form of raised liver enzymes and HBV DNA PCR 1 month after DAA therapy (Table 1). On liver-function tests, all patients showed decreased mean ALT at 1 month, 3 months, 6 months, and 12 months post-treatment: 24.9 $\pm$  14.2, 24.4 $\pm$ 10.8, 23 $\pm$ 8.2, and 13.2 $\pm$ 3.5 U/L, respectively ( $P=0.001$ ). Significant improvement in AST levels was also detected, reaching 13.7 $\pm$ 3.5 U/L at 1 year posttherapy. ( $P=0.001$ ). Bilirubin, INR, and platelet counts showed significant improvement at 1 year posttreatment (Table 2, Figures 1 and 2). Patients showed decreased mean HBV PCR levels: from 913.4 $\pm$ 1,362.4 IU/mL (before treatment) to 760.8 $\pm$ 379.02 IU/mL (6 months after starting treatment) and 396.1 $\pm$ 124.8 IU/mL (12 months after starting treatment).

**Table 1** Demographic Data Of Studied Patients

	Patients (n=140)
<b>Age (years), mean <math>\pm</math> SD</b>	32.44 $\pm$ 8.02
<b>Sex, n (%)</b>	
Male	96 (68.6%)
Female	44 (31.4%)
<b>FibroScan, n (%)</b>	
F0	77 (55%)
F1	63 (45%)
<b>HBV-reactivated patients (n=4)</b>	
<b>Age (years), mean <math>\pm</math> SD</b>	23.75 $\pm$ 2.75
<b>Sex</b>	
Male	3 (75%)
Female	1 (25%)

For liver-function tests in patients with HBV reactivation, AST levels before treatment and at 1 month, 3 months, 6 months, and 12 months after starting DAA therapy were 29.7 $\pm$ 2.2, 60.3 $\pm$ 4.8, 71.5 $\pm$ 5.8, 23.3 $\pm$ 0.5, and 11.5 $\pm$ 3.3 U/L, respectively, with a significant decrease at 12 months posttreatment ( $P=0.001$ ). ALT was 25.8 $\pm$ 5.5, 68.5 $\pm$ 5.1, 65.2 $\pm$ 8.3, 11.8 $\pm$ 4.9, and 10.0 $\pm$ 1.4 U/L before treatment and at 1 month, 3 months, 6 months, and 1 year after DAA therapy, respectively, with significant improvement ( $P=0.001$ ). Bilirubin and INR both showed significant 1-year posttreatment improvement ( $P=0.001$ ). Quantitative HBV DNA PCR in patients with HBV reactivation during DAA therapy was raised at 1 month (10,184.5 $\pm$ 1,857.2 IU/mL) and 3 months (20,802 $\pm$ 1,059.7 IU/mL) after starting DAAs. HBV PCR then gradually decreased (without HBV antiviral therapy) until finally becoming undetectable 1 year posttherapy (6 months after the end of DAA therapy,  $P=0.001$ ). At 1 year post-treatment, platelet counts showed significant increase: from 183 $\pm$ 4.2 $\times 10^3/\mu$ L (before treatment) to 202.3 $\pm$ 2.2 $\times 10^3/\mu$ L (1 year posttreatment;  $P=0.001$ ; Table 2, Figures 3 and 4). All patients had negative HCV PCR at 1 month posttreatment, and all had achieved sustained virologic response with negative HCV PCR 3 months after the end of treatment.

## Discussion

The reactivation of HBV means detection of de novo HBV DNA not previously detected, a 1–2 log IU/mL increase in serum HBV DNA, or lasty seroconversion in individuals with HBc Ab.<sup>13</sup> Studies concerned with the reactivation of

**Table 2** Comparisons Of ALT, AST, And HBV PCR (Before Chronic Hepatitis C Virus Treatment, 1 Month, 3 Months, And 6 Months After Therapy)

	Before	After 1 Month	After 3 Months (End Of Treatment)	After 6 Months	After 12 Months	P-value
<b>Platelets (<math>10^3/\mu\text{L}</math>), mean <math>\pm</math> SD</b>	181.1 $\pm$ 64.5	201.5 $\pm$ 59.7	203.5 $\pm$ 53.6	210.5 $\pm$ 52.7	221.3 $\pm$ 53.1	0.001
<b>Bilirubin (mg/dL), mean <math>\pm</math> SD</b>	1.2 $\pm$ 0.5	1.2 $\pm$ 0.3	1.12 $\pm$ 0.2	1.01 $\pm$ 0.1	0.9 $\pm$ 0.1	0.001
<b>AST (U/L), mean <math>\pm</math> SD</b>	23.3 $\pm$ 8.3	24.8 $\pm$ 9.7	25.4 $\pm$ 10.5	22.3 $\pm$ 8.3	13.7 $\pm$ 3.5	0.001
<b>ALT (U/L), mean <math>\pm</math> SD</b>	29.7 $\pm$ 39.1	24.9 $\pm$ 14.2	24.4 $\pm$ 10.8	23 $\pm$ 8.2	13.2 $\pm$ 3.5	0.001
<b>INR, mean <math>\pm</math> SD</b>	1.3 $\pm$ 0.11	1.2 $\pm$ 0.12	1.05 $\pm$ 0.1	0.9 $\pm$ 0.1	0.9 $\pm$ 0.1	0.001
<b>HBV PCR (IU/mL), mean <math>\pm</math> SD</b>	913.4 $\pm$ 1,362.4	1,395.4 $\pm$ 2,619.3	2,282.8 $\pm$ 5,415.4	760.8 $\pm$ 379.02	396.1 $\pm$ 124.8	0.049
<b>HBV-reactivated patients (n=4)</b>						
<b>Platelets (<math>10^3/\mu\text{L}</math>), mean <math>\pm</math> SD</b>	183 $\pm$ 4.2	183 $\pm$ 2.9	194.2 $\pm$ 4.3	196.3 $\pm$ 2.2	202.3 $\pm$ 2.2	0.001
<b>Bilirubin (mg/dL), mean <math>\pm</math> SD</b>	1.27 $\pm$ 0.17	1.4 $\pm$ 0.08	1.35 $\pm$ 0.05	1.01 $\pm$ 0.01	0.9 $\pm$ 0.05	0.001
<b>AST (U/L), mean <math>\pm</math> SD</b>	29.7 $\pm$ 2.2	60.3 $\pm$ 4.8	71.5 $\pm$ 5.8	23.3 $\pm$ 0.5	11.5 $\pm$ 3.3	0.001
<b>ALT (U/L), mean <math>\pm</math> SD</b>	25.8 $\pm$ 5.5	68.5 $\pm$ 5.1	65.2 $\pm$ 8.3	11.8 $\pm$ 4.9	10.0 $\pm$ 1.4	0.001
<b>INR, mean <math>\pm</math> SD</b>	1.2 $\pm$ 0.12	1.2 $\pm$ 0.09	1.1 $\pm$ 0.05	0.9 $\pm$ 0.03	0.8 $\pm$ 0.02	0.001
<b>HBV PCR (IU/mL), mean <math>\pm</math> SD</b>	1,494 $\pm$ 571	10,184.5 $\pm$ 1,857.2	20,802 $\pm$ 1,059.7	666 $\pm$ 148.6	—	0.001

Notes:  $P < 0.05$  considered significant;  $P < 0.001$  considered highly significant.

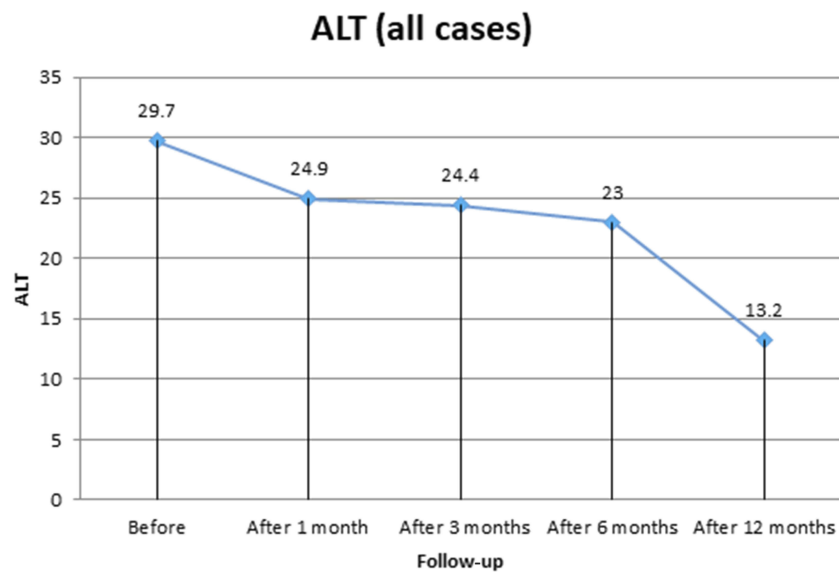
HBV after DAA treatment for HCV have given different results over the past few years. It is postulated that HCV infection suppresses HBV replication through many HCV core proteins, such as NS5Aa and NS2.<sup>14–19</sup> This is why suppression of HCV by DAA is postulated to increase HBV replication. This was manifested in our data, where after 1 month of treatment there was marked elevation in HBV DNA.

In a cohort study on chronic HCV patients with positive HBsAg who underwent DAAs in Egypt, the risk of reactivation in the absence of HBV treatment was 28.6% (95% CI 15.6%–46.4%) and the risk of hepatitis in the patients who experienced reactivation 10.0% (95% CI 0.9%–57.8%). Also, the pooled risk of reactivation in HBsAg-negative anti-HBc-positive patients was negligible (0.1%, 95% CI 0–0.3%), irrespective of the presence of anti-HBs.<sup>20</sup>

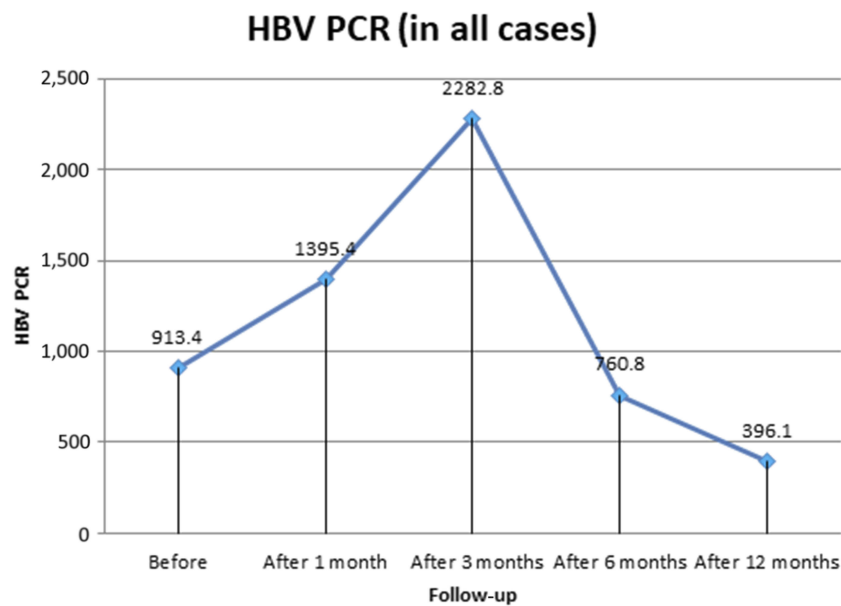
We studied patients that were coinfecting with HCV–HBV. All patients had HBV PCR  $< 2,000$  IU/mL and showed HBeAg seroconversion with development of

HBeAb. From the 140 patients studied, only four showed HBV reactivation, representing 2.8% of the studied group. When we followed all patients after DAA therapy, there were significant decreases in liver enzymes and HBV DNA. This was similar to a study that showed a decrease in liver enzymes after treatment of HCV, but without the statistical significance found in our study. Also, that study counted on quantitative HbcAb to diagnose the condition, while we tested patients for seroconversion of HbeAg, but not quantitative HbcAb.<sup>21</sup> It is known that the HBeAg seroconversion is associated with low levels of HBV DNA, with clinical improvement in liver disease in the majority of patients.<sup>22–25</sup> This was the case in our patients, where a significant decrease was observed in liver enzymes that was associated with a decrease in HBV DNA.

In a meta-analysis, Chen et al compared the rate of reactivation in patients with chronic HBV versus those with occult infection. One of the results of the study was



**Figure 1** ALT in all included patients.



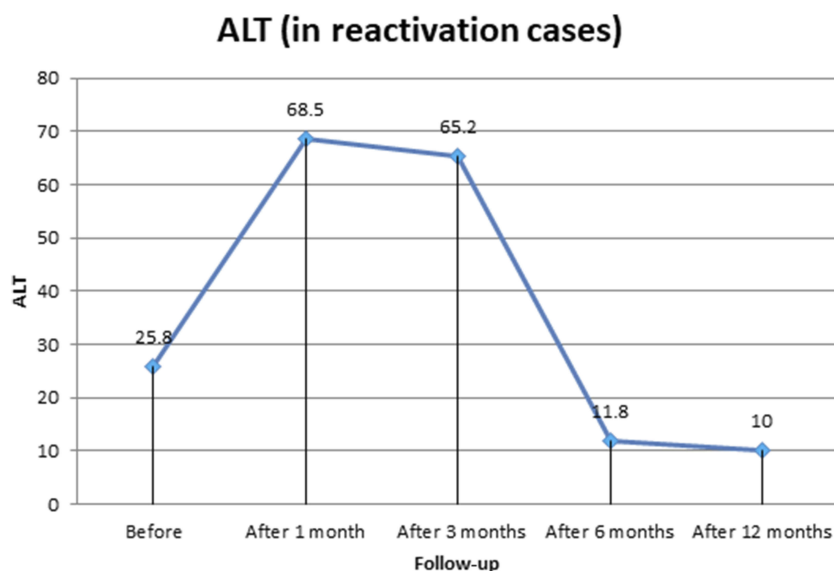
**Figure 2** HBV PCR in all included patients.

that HBV reactivation and hepatitis were less common among individuals with occult HBV infection.<sup>26</sup> This was in concordance with our study. In another study investigating 848 individuals treated with DAAs, only eight patients showed detectable HBV DNA with titers <20 IU/mL at the end of treatment, and no HBV reactivation was observed in HBsAg-negative but anticore-positive patients.<sup>27</sup>

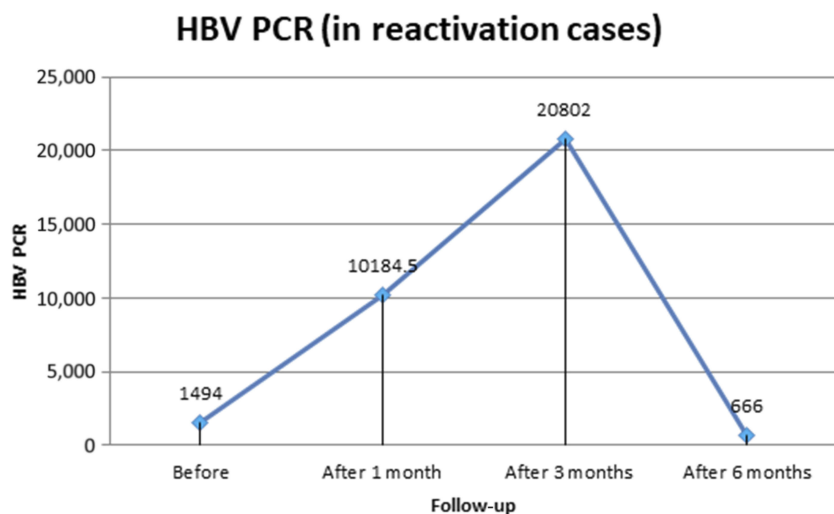
HBV reactivation was manifested in our study by elevated liver enzymes and increasing HBV DNA in four patients. This rise had resolved at 6-month of follow up

without adding antiviral treatment for HBV. This was the case in another study where elevated ALT was present in 18 patients during follow-up of 108 patients coinfecting with HCV-HBV.<sup>28</sup> In a 72-year-old woman, HBV reactivation was observed 4 weeks after the end of treatment with sofosbuvir and ribavirin with resolved HBV.<sup>29</sup> This was similar to our study, where resolution of the four reactivated cases occurred with no treatment.

In our study, we conclude that patients with F0 or F1, HBeAg seroconversion, and HBV DNA <2,000 IU/mL



**Figure 3** ALT in HBV reactivation patients.



**Figure 4** HBV PCR in hepatitis B reactivation patients.

can complete without treatment with close monitoring. Also, the risk of HBV reactivation is low in patients treated with DAAs. Being a prospective study with close monitoring of the patients gives strength to our work. Still, we need longer follow-up and larger samples.

## Disclosure

The authors report no conflicts of interest in this work.

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