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**Risk of hepatitis B reactivation in patients treated with direct-acting antivirals for hepatitis C**

Aggeletopoulou I *et al.* HBV reactivation during direct-acting antiviraltreatment

Ioanna Aggeletopoulou, Christos Konstantakis, Spilios Manolakopoulos, Christos Triantos

**Ioanna Aggeletopoulou, Christos Konstantakis, Christos Triantos,** Department of Gastroenterology, University Hospital of Patras, 26504 Patras, Greece

**Spilios Manolakopoulos,** 2ndDepartment of Internal Medicine, Hippokration General Hospital of Athens, 11527 Athens, Greece

**Author contributions:** Aggeletopoulou I collection data and drafting the manuscript; Konstantakis C collection data; Manolakopoulos S interpretation of the data, drafting the manuscript, and revision of manuscript for important intellectual content; Triantos C interpretation of the data, drafting the manuscript, and revision of manuscript for important intellectual content

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**Correspondence to: Christos Triantos, MD,** Department of Gastroenterology, University Hospital of Patras, D. Stamatopoulou 4, Rio 26504, Patras, Greece. chtriantos@hotmail.com

**Telephone**: +30-697-2894651

**Fax**: +30-261-0625382

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**Abstract**

The recent introduction of direct-acting antiviral drugs (DAAs) for treatment of the hepatitis C virus (HCV) has greatly improved the management of HCV for infected patients. These viral protein inhibitors act rapidly, allowing HCV clearance and increasing the sustained virological response rates. However, hepatitis B virus HBV reactivation has been reported in HCV/HBV co-infected patients. Hepatitis B reactivation refers to an abrupt increase in the hepatitis B virus and is well-documented in patients with previously undetected HBV DNA due to inactive or resolved HBV infection. Reactivation can occur spontaneously, but in most cases, it is triggered by various factors. Reactivation can be transient, without clinical symptoms; however, it usually causes a hepatitis flare. HBV reactivation may occur regardless of HCV genotype and type of DAA regimen. HBV screening is strongly recommended for co-infected HCV/HBV patients before initiation of and during DAA therapy regardless of HBV status, HCV genotype and class of DAAs used. HBV reactivation can be prevented with pretreatment screening and prophylactic treatment when necessary. Additional data are required to evaluate the underlying mechanisms of HBV reactivation in this setting.

**Key words:** Hepatitis B; Hepatitis C; Hepatitis B virus reactivation; Direct-acting antivirals; Pretreatment screening

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**Core tip:** Hepatitis B reactivation is related to an abrupt increase in hepatitis B virus (HBV) replication in patients with inactive or resolved hepatitis B. Most cases of HBV reactivation resolve spontaneously, but the existence of continuous immune suppression leads to hepatitis flare development and then to progressive acute hepatic injury. The introduction of direct-acting antiviral drugs (DAAs) treatment increases the risk of HBV reactivation in hepatitis C virus (HCV) /HBV co-infected patients. The high incidence of HBV reactivation in these patients highlights the necessity for HBV pretreatment screening before initiation of and during DAA therapy.

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**INTRODUCTION**

Epidemiological studies suggest that approximately 240 million people worldwide are infected with the hepatitis B virus (HBV)[[1](#_ENREF_1),[2](#_ENREF_2)]. The clinical course of HBV infection varies and may include asymptomatic carriage, acute hepatitis or chronic active hepatitis, which can progress to cirrhosis and hepatocellular carcinoma[[2](#_ENREF_2),[3](#_ENREF_3)].

HBV reactivation is characterized by an increase of HBV DNA in the serum and is well documented in patients with previously undetected HBV DNA, due to inactive or resolved HBV infection[[4-6](#_ENREF_4)]. Reactivation is usually followed by the reappearance of HBV activity (HBV DNA recurrence or increase > 1 log) or a flare of hepatitis in previously minimal or inactive disease[[5](#_ENREF_5)]. HBV reactivation mainly occurs in patients who receive immunosuppressive or cytotoxic chemotherapy for various malignancies[[6-8](#_ENREF_6)] and autoimmune diseases[[9-12](#_ENREF_9)] or in patients who undergo solid organ transplantation[[13](#_ENREF_13),[14](#_ENREF_14)]. The reappearance of serum HBV DNA has also occasionally been observed in patients with the hepatitis B surface antigen (HBsAg) seroclearance, suggesting that HBV reactivation occurs in patients who have recovered from hepatitis B and have antibodies for the hepatitis B core antigen (anti-HBc) but have no detectable serum HBsAg[[15](#_ENREF_15),[16](#_ENREF_16)].

Hepatitis with alanine transaminase (ALT) elevation due to reactivation of HBV has been reported in HCV/HBV co-infected patients who were treated with direct-acting antiviral (DAA) regimens for chronic hepatitis C virus (HCV) infection[[17-23](#_ENREF_17)]. Patients with HCV/HBV coinfection have a significantly higher risk of developing hepatic cirrhosis and hepatocellular carcinoma[[24](#_ENREF_24)]. In HCV/HBV coinfection, HCV has been shown to suppress HBV replication, resulting in decreased HBV antigen levels[[21](#_ENREF_21),[25](#_ENREF_25)]. The administration of HCV treatment may lead to an increase in HBV replication and in lower rates of HBV DNA clearance. Pegylated interferon (Peg-IFN)-based treatments could suppress both HCV and HBV replication[[26](#_ENREF_26),[27](#_ENREF_27)]. However, the development of interferon-free treatments with DAA agents has changed the course of treatment for chronic HCV infection[[28](#_ENREF_28)]. DAAs constitute new therapeutic agents with great efficacy for the treatment of HCV infection, and they can be used safely in HCV naïve-treatment patients or in patients who have been treated unsuccessfully, thus decreasing the duration of therapy, improving the sustained virological response rates and reducing side effects[[28-30](#_ENREF_28)].

**PATHOGENESIS OF HBV REACTIVATION**

Chronic HBV infection is defined as persistent circulating serum HBsAg for more than 6 mo[[31](#_ENREF_31),[32](#_ENREF_32)]. In the initial stages of immune tolerance, HBV replication is enhanced by the presence of increased levels of HBeAg and active infection of hepatocytes[[31](#_ENREF_31),[33](#_ENREF_33)]. The maturation of the immune system leads to the clearance phase, which is characterized by T cell mediated damage of infected hepatocytes through immune surveillance and the development of hepatitis flares[[31](#_ENREF_31),[33](#_ENREF_33)]. Spontaneous HBeAg clearance is followed by the suppression of HBV DNA and the increase of circulating ALT levels[[31](#_ENREF_31),[33](#_ENREF_33)]. During the immune control phase, some patients achieve HBV DNA clearance and develop immunoprotection[[31](#_ENREF_31)]. However, when a patient is exposed to immunosuppressive agents or has concomitant infection with HIV, HCV, HAV or HDV, loss of immune control occurs, and there is an increased risk of HBV reactivation. HBV reactivation may be spontaneous and is divided into 3 different phases[[4](#_ENREF_4),[5](#_ENREF_5),[31-35](#_ENREF_31)]. An abrupt increase of HBV replication occurs with a concomitant development of an infection in the hepatocytes and with the reappearance of HBV markers (HBsAg and HBeAg). At the second phase, immunosuppression is reduced and hepatocytes are targeted and damaged, causing liver injury that can range from mild to fulminant, or fatal hepatitis. This phase is followed by the recovery phase, in which liver damage is resolved[[4](#_ENREF_4),[5](#_ENREF_5),[31-35](#_ENREF_31)]. HBV reactivation can lead to progressive hepatic injury and even hepatic decompensation[[16](#_ENREF_16)].

**REACTIVATION OF HEPATITIS B IN HCV INFECTED PATIENTS**

Recent studies have shown that there is a risk of HBV reactivation in patients with HCV and HBV coinfection, who receive treatment with direct-acting antivirals[[17-21](#_ENREF_17),[23](#_ENREF_23)]. There are 5 case reports[[17-21](#_ENREF_17)], 1 observational study[[23](#_ENREF_23)] and 1 letter to the editor[[22](#_ENREF_22)] that describe the HBV reactivation in HCV/HBV co-infected patients following the use of DAA regimens. The clinical characteristics of the patients involved in these studies are shown in Table 1. Collins et al. reported 2 cases of HBV reactivation during HCV treatment using sofosbuvir and simeprevir regimens[[21](#_ENREF_21)]. At the initiation of the treatment, the HBV DNA viral load was 2.300 IU/mL for the first patient and was under the lower limit of 20 IU/mL for the second patient. At 4 wk, HCV clearance had been achieved in the first patient, but at week 8, the HBV viral load had significantly increased to 22 million IU/mL. At week 2, the second patient had an undetectable HCV viral load, but at week 4, the HBV viral load increased to 11.255 IU/mL. Both patients received HBV treatment consisting of either tenofovir/emtricitabine or tenofovir[[21](#_ENREF_21)]. Ende *et al*[[20](#_ENREF_20)]described a case of HBV reactivation in an HCV patient who was HBsAg negative but anti-HB core positive. The patient received HCV treatment with sofosbuvir, simeprevir and ribavirin and had an HCV viral load below the level of quantification at 4 wk after treatment. The HBV viral load was undetectable before the initiation of the treatment, but at week 11 of a planned 12-week course, the patient developed severe hepatitis B with a viral load of 29 million IU/mL and started a treatment using tenofovir[[20](#_ENREF_20)]. Takayama *et al*[[17](#_ENREF_17)] reported one case of HBV reactivation in a patient who was an inactive carrier of HBV with a viral load of 310 IU/mL prior to HCV treatment. He received a combination of daclatasvir/asunaprevir and the HCV RNA on day 15 was undetectable. On day 43, serum HBV DNA increased to 10 million IU/ml. A hepatitis flare due to HBV reactivation was diagnosed and the patient received entecavir[[17](#_ENREF_17)]. De Monte *et al*[[19](#_ENREF_19)] reported a case of HBV reactivation in a patient who had a resolved HBV infection and chronic HCV/HIV coinfection and was on a treatment combination of DAAs (sofosbuvir/ledipasvir). Upon initiation of the treatment, the patient had an undetectable HBV viral load. At week 6, the HBV viral load had increased (960 million IU/mL) and tenofovir was introduced[[19](#_ENREF_19)]. Hayashi *et al*[[18](#_ENREF_18)] reported a case of a patient with unclear HBV infection status who was infected with HCV. The patient received an HCV treatment consisting of daclatasvir/asunaprevir, and 4 wk after initiation of the treatment, the HCV RNA became negative. Five months after treatment began, the patient developed acute hepatitis B and initiated treatment with entecavir for suspected liver failure due to HBV reactivation[[18](#_ENREF_18)]. Madonia *et al*[[22](#_ENREF_22)] reported a case of HBV reactivation in a patient with HCV infection and isolated anti-HBc, who was being treated with sofosbuvir/ribavirin. Thirty-six weeks after the initiation of the DAA therapy, the patient developed a hepatitis flare and started tenofovir treatment[[22](#_ENREF_22)]. The incidence of HBV reactivation in HCV/HBV co-infected patients was further confirmed in an observational study that was conducted in China[[23](#_ENREF_23)]. Ten patients in the study were HBsAg positive before initiation of the HCV treatment, and 3 (30%) of them developed HBV reactivation after the use of DAA regimens[[23](#_ENREF_23)]. In contrast, none of the 124 patients with occult HBV infection developed HBV reactivation during the use of DAA regimens[[23](#_ENREF_23)].

**DISCUSSION**

Various concerns have been raised in relation to the reappearance of hepatitis B due to HBV reactivation after successful clearance of hepatitis C through the use of DAA therapy in patients with HCV/HBV coinfection[[17-23](#_ENREF_17),[36](#_ENREF_36),[37](#_ENREF_37)]. Recently, clinical and in vitro studies have been carried out to elucidate the virological and molecular aspects of the HCV/HBV coinfection[[17-23](#_ENREF_17)]. The clinical characteristics of the patients in these studies vary, as they were infected with different HCV genotypes, received different oral DAA regimens and presented with various states of HBV infection[[17-23](#_ENREF_17)]. However, none of the patients received HBV treatment concurrently with DAA therapy, and all of the patients had increased serum HBV DNA after or at the end of the HCV treatment[[17-23](#_ENREF_17)]. This suggests that HCV RNA clearance may be associated with HBV reactivation, regardless of HCV genotype and type of DAA regimen.

There are data supporting that there is a significant increase in hepatitis due to HBV reactivation in HCV patients who are also HBsAg positive and are being treated with DAA therapy[[23](#_ENREF_23)]. Wang *et al*[[23](#_ENREF_23)] reported that HCV patients with HBV or occult HBV infection who are receiving DAA therapy may develop a biochemical flare that is unrelated to HBV reactivation[[23](#_ENREF_23)]. Other causes, such as ingesting herbs and binge drinking alcohol were the main causes of hepatitis development in these cases.

The molecular aspects related to HCV/HBV interferences remain controversial, as patients with HCV/HBV coinfection show a high range of virological profiles. Several studies have described an inverse relationship between the DNA levels of the two viruses in cases of coinfection, suggesting potential direct or indirect viral interference in their life cycle[[19](#_ENREF_19),[26](#_ENREF_26),[38-40](#_ENREF_38)]. In particular, most HBV-infected individuals who develop HCV have decreased HBV replication due to the suppression effect of HCV on HBV infection[[39](#_ENREF_39),[41](#_ENREF_41)]. Similarly, suppression in HCV replication occurred in patients who developed an HBV superinfection[[38](#_ENREF_38),[41](#_ENREF_41)]. Other studies have reported HBV reactivation in patients with HCV/HBV after treatment with peginterferon/ribavirin[[42](#_ENREF_42),[43](#_ENREF_43)]. In addition, studies that included in vitro experiments with HCV/HBV co-transfection in the same cell culture system, have shown that HCV and HBV were able to replicate in the same hepatocyte without evidence of interference[[44](#_ENREF_44),[45](#_ENREF_45)]. Lastly, another study supports the theory that in the chronically HCV-infected liver, the HCV-induced IFN-α/β response creates an antiviral state that limits both the initiation of HBV infection and the replication of HBV in the cells whose type I interferon-stimulated gene expression profile does not preclude HBV infection[[16](#_ENREF_16)]. The above data suggest that the viral interference and the various dominance phases in co-infected patients may occur due to an indirect mechanism mediated by host immune regulation[[26](#_ENREF_26)].

The HBV reactivation in the examined studies was a retrospective diagnosis in most cases[[17-22](#_ENREF_17)]. Collins *et al*[[21](#_ENREF_21)] described two different cases of HBV reactivation that occurred in the same medical unit. In the second case, diagnosis was earlier due to a previous case of HBV reactivation. After initiation of the DAA treatment, the HBV DNA concentrations were prospectively monitored at 2-week intervals, and when HBV replication had logarithmically increased, anti-HBV therapy was initiated[[21](#_ENREF_21)]. Consequently, the HBV viral load should be closely monitored during HCV treatment using DAAs in patients that have an HCV/HBV coinfection to prevent the progression to HBV reactivation. Moreover, the observational study done by Wang et al. prospectively evaluated the incidence of HBV reactivation in Chinese patients who were HCV/HBV co-infected and receiving DAA treatment regimens[[23](#_ENREF_23)]. Wang *et al*[[23](#_ENREF_23)] concluded that patients with HCV infection and HBsAg positivity are at greater risk of developing HBV reactivation, and thus they strongly suggest that HBsAg status be checked before the initiation of pan-oral DAA therapy. However, it is worth-mentioning that we did not find any cases with fatal outcomes due to reactivation.

 The cases of HBV reactivation in co-infected HCV/HBV patients who are undergoing DAA treatment support the theory of reciprocal HCV/HBV interference and suppression of HBV replication due to HCV infection. Interferon-based anti-HCV therapies have rarely led to HBV reactivation due to their suppression effect on both HBV and HCV replication[[27](#_ENREF_27)]. The introduction of DAA treatment increased the risk of HBV reactivation because of HCV clearance and lack of anti-HBV activity. This eliminates the inhibitory effects of HCV on HBV, leading to HBV reactivation. These data suggest that after initiation of DAA treatment, HBV infection should be closely monitored in co-infected patients by checking the HBV viral load, the HBsAg and the aminotransferase levels, regardless of the type of DAAs and the HCV genotype. In patients with positive anti-HBc and negative HBsAg and anti-HBs, the HBV viral load could be measured before the initiation of DAAs and should be monitored during the treatment. Anti-HBV therapy should be considered when the HBV viral load is detected after the initiation of DAA therapy. Patients with liver cirrhosis or impaired liver function are at greater risk and an HBV reactivation occurrence may be fatal. Therapy with NAs could prevent adverse effects, such as severe liver failure, when the HBV reactivation is diagnosed at an early stage. Recent guidelines on this issue have been introduced by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD)[[36](#_ENREF_36),[37](#_ENREF_37)]. EASL guidelines suggest that patients should be tested for HBs antigen, anti-HBc and anti-HBs antibodies before the initiation of DAA therapy[[36](#_ENREF_36)]. If HBs antigen is present, or if HBV DNA is detectable in HBs antigen-negative, anti-HBc antibody-positive patients (“occult” hepatitis B), then concurrent HBV NA therapy is indicated[[36](#_ENREF_36),[46](#_ENREF_46)]. AASLD suggests that all HCV patients who are about to initiate DAA therapy should be assessed for HBV coinfection by checking for the presence of HBsAg, anti-HBs and anti-HBc[[37](#_ENREF_37)]. In addition, patients with positive HBsAg should be tested for HBV DNA viral load prior to the initiation of DAA therapy[[37](#_ENREF_37)]. The patients who meet the criteria for HBV treatment due to active HBV infection should initiate the HBV treatment before or during the HCV treatment[[37](#_ENREF_37)]. The patients with low or undetectable HBV DNA levels should be monitored at regular intervals (usually no more than once every 4 weeks) for HBV reactivation, and the patients with HBV DNA levels that meet treatment criteria should initiate HBV therapy[[37](#_ENREF_37)]. For those patients with positive anti-HBc or anti-HBs and anti-HBc, there are no sufficient recommendations; however, there is a risk of HBV reactivation in the case of elevated liver enzymes during or after DAA therapy[[37](#_ENREF_37)]. In everyday clinical practice, patient characteristics [age, co morbidities (especially liver–related, such as alcohol use and obesity), performance status, liver function status/presence of cirrhosis, HIV status] and institutional/national regulations and insurance policies are critical for decisions regarding treatment. Moreover, that HBV reactivation does not occur during DAA treatment as often as with other immunosuppressive therapies, should further impact the decision for treatment. Taking the safety of the patients into serious consideration, we could propose the “treat first” strategy for patients with poor performance status and advanced fibrosis (Figure 1).

**CONCLUSION**

Generally, HBV reactivation is a severe, life-threatening consequence of chemotherapy and immunotherapy in patients with chronic hepatitis B infection. The severity of HBV reactivation ranges from mild with asymptomatic elevation of aminotransferases to fulminant liver failure. Recent evidence suggests that reactivation may be associated with DAA therapy in patients with HCV/HBV coinfection. HBV screening is recommended for patients both before the initiation of and during DAA therapy. HBV reactivation can be prevented through the use of pretreatment screening and anti-HBV prophylactic treatment. Existing evidence is not enough to support pre-emptive therapy in all patients with HBsAg or occult hepatitis B. Additional studies are needed to investigate the duration of HBV treatment and the potential alternative HCV antiviral treatments in HCV/HBV co-infected patients to eliminate the risk of HBV reactivation. Moreover, further studies should be conducted to evaluate the underlying mechanisms of HBV reactivation during DAA therapy that is deemed necessary. Until then, careful monitoring for HBV reactivation should be mandatory both before and during anti-HCV therapy with DAA.

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**Table 1** **Overview of clinical characteristics in patients with hepatitis C virus /** **hepatitis B virus coinfection who had hepatitis B virus reactivation during direct-acting antiviral drugs -based hepatitis C virus treatment**

|  |  |  |
| --- | --- | --- |
| Patients’ characteristics | HCV Treatment | HBV Infection |
| Ref  | **Gender** | **Age** | **HIV coinfection** | **HCV genotype** | **Previous treatment** | **DAA regimen** | **Profile before DAAs1** | **HBV DNA (IU/mL) before/after DAAs2** | **ALT levels (IU/L) before/after DAAs3** | **Week4** |
| Collins *et al*[[21](#_ENREF_21)] | M | 55 | No | 1a | IFN/ribavirin | sofosbuvir/simeprevir | Inactive carrier | 2.300/22 million | 62/1.495 | 8 |
| Collins  *et al*[[21](#_ENREF_21)] | M | 57 | No | 1a | IFN/ribavirin | sofosbuvir/simeprevir | Occult infection | 20/11.255 | Within normal limits | 4 |
| Ende  *et al*[[20](#_ENREF_21)] | F | 59 | No | 1b | IFN/ribavirin | sofosbuvir/simeprevir/ribavirin | Resolved infection | Undetectable/ 29 million | 168/2.263 | 11 |
| Takayama  *et al*[[17](#_ENREF_21)] | M | 69 | No | 1b | No treatment | daclatasvir/asunaprevir | Inactive carrier | 310/10 million | 94/237 | 6 |
| De Monte  *et al*[[19](#_ENREF_21)]  | M | 53 | Yes | 4d | IFN/ribavirin | sofosbuvir/ledipasvir | Resolved infection | Undetectable/ 960 million | Within normal limits /1.026 | 6 |
| Hayashi  *et al*[[18](#_ENREF_21)] | F | 83 | No | 1b | No treatment | daclatasvir/asunaprevir | Unclear | Undetectable/ 1.000.000 | Within normal limits/1.066 | 48 |
| Madonia  *et al*[[22](#_ENREF_21)] | F | 62 | No | 2 | No treatment | sofosbuvir/ribavirin | Resolved infection | Undetectable/ 2.080.000 | 34/1.896 | 36 |

1Profile of HBV infection according to HBV viral load and HBs antigen detection; 2HBV viral load before DAA treatment and at initiation of HBV reactivation; 3ALT levels before DAA treatment and at initiation of HBV reactivation; 4Weeks after the initiation of DAA treatment. HIV: Human immunodeficiency virus; HCV: Hepatitis C virus; HBV: Hepatitis B virus; IFN: Pegylated interferon; ALT: Alanine transaminase; DAA: Direct-acting antiviral drugs.



**Figure 1** **Treatment algorithm.** Therapeutic options for HCV-HBV co-infected patients. All HCV patients who are about to commence DAA therapy should be assessed for HBV coinfection and accordingly for HDV. Patients who are negative for HBV will be monitored using liver function tests (LFTs) during and after the end of DAA therapy. A flare in ALT/liver biochemistry during this timeframe should prompt the treating physician to reconsider the possibility of an occult HBV infection and to re-test for HBV infection (HBsAg and/or HBV DNA)[[36](#_ENREF_36)]. Management options for patients who are positive for HBV vary according to their serology results. HBsAg positive patients have the following two options: the “treat first” approach (blue pathway), where HBsAg positive are treated with NA agents (commencing NA therapy even before the start of DAA treatment), or the “test first” option (green pathway) where patients are monitored with HBV DNA and are treated according to the detected levels. Both treatment options are viable and are supported by clinical guidelines[[36](#_ENREF_36),[37](#_ENREF_37)]. HCV: Hepatitis C virus; DAA: Direct-acting antiviral; Tx: Therapy; HDV: Hepatitis D virus; CHB: Chronic hepatitis B infection; HBsAg: Hepatitis B surface antigen; anti-HBs: Hepatitis B surface antibody; anti-HBc: Total hepatitis B core antibody; NA: Nucleoside/nucleotide analogue; LFTs: Liver function tests; ALT: Alanine transaminase; blue pathway, options in accordance with EASL guidelines; green pathway, options in accordance with AASLD - IDSA guidelines.

Hepatitis C virus (HCV)

Hepatitis B virus (HBV)