Revista Portuguesa de Doenças Infecciosas
Relato de Casos Clínicos
Relato de Casos Clínicos / Case Reports 2026 – Volume 20 – Número 2

HBsAg loss after hepatitis B reactivation in a patient with hepatitis C treated with direct-acting antivirals

Perda de AgHBs após reativação da hepatite B em doente com hepatite C tratada com antivíricos de ação direta

Cristina Valente[1], Ruben Carvalho[1]

[1] Department of Infectious Diseases, Unidade Local de Saúde de Coimbra, Coimbra, Portugal

Autor correspondente: Cristina Valente **Email: cristinaasvalente@gmail.com**

DOI: 10.65332/rpdi.v20.150 **Recebido: 05 mai 2026** **Aceite: 18 jul 2026** **Publicado: 11 set 2026**

ABSTRACT

Introduction: Hepatitis B virus (HBV) reactivation has been reported in patients treated with direct-acting antiviral (DAA) agents for chronic hepatitis C virus infection. It also remains controversial whether it is necessary to administer nucleos(t)ide analogues for anti-HBV therapy. The outcome of HBV reactivation is not fully understood, and HBsAg seroclearance may occur.

Case Presentation: We report a rare case of HBsAg loss following HBV reactivation, without hepatic flares, in an HBsAg-positive, anti-HCV-positive, and HCV RNA-positive patient, treated with DAA. Due to undetectable HBV DNA and low HBsAg levels before DAA initiation, no HBV treatment was initiated.

Discussion: It remains unclear whether the clinical course would have been the same had treatment for hepatitis B been initiated at the time of HBV reactivation.

Conclusion: Current data suggest treatment should be considered for all HBsAg-positive patients when they start DAA, even in those who fail to meet treatment criteria, given the risk of reactivation.

Keywords: Hepatitis B reactivation; HBsAg loss; Hepatitis C treatment; Direct-acting antiviral.

 — © 2026 The Author(s). CC BY 4.0

RESUMO

Introdução: A reativação da hepatite B tem sido descrita durante ou após o tratamento da hepatite C com antivíricos de ação direta (AAD). Continua a existir alguma controvérsia sobre quem tratar com análogos dos nucleós(t)idos, no momento do tratamento com AAD. O mecanismo de reativação do vírus da hepatite B (VHB) e a interação entre estes dois vírus não estão completamente esclarecidos e, embora rara, a clearance de AgHBs pode ocorrer.

Descrição do Caso: Descreve-se um caso de uma doente AgHBs/anti-VHC e ARN VHC positivos, que sofreu reativação da hepatite B, seguida de perda de AgHBs, no decurso do tratamento de hepatite C, e que apresentava ADN VHB indetetável e valor baixo de AgHBs quantitativo prévios ao tratamento da hepatite C.

Discussão: Questiona-se se a evolução teria sido a mesma no caso de ter sido instituído tratamento para a hepatite B, no momento da reativação do VHB.

Conclusão: A literatura sugere que, mesmo sem haver critérios para tratamento da hepatite B, esta hipótese deve ser considerada, atendendo ao risco de reativação.

Palavras-Chave: Reativação da hepatite B; Perda de AgHBs; Tratamento da hepatite C; Antivíricos de ação direta.

Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) can both cause chronic infection and lead to cirrhosis and hepatocellular carcinoma[1]. HBV/HCV coinfection may occur, but this interplay is not fully understood[2], as the intracellular interactions of the two viruses are unclear.

In HBV-monoinfected patients, functional cure, characterised by HBsAg (hepatitis B surface antigen) seroclearance, is the treatment goal of chronic HBV infection[3], but its annual incidence is <1%, regardless of antiviral nucleos(t)ide analogue (NA) therapy[4]. Spontaneous HBsAg loss occurs infrequently (about 1.0–2.0% per year) in treatment-naïve adult patients with chronic HBV-monoinfection. The loss of HBsAg is a complex immune process that involves cell-mediated immune responses, antibody production, and the formation of immune memory[5]. In some patients, the immune system is able to successfully clear HBV by recognizing and eliminating infected hepatocytes or neutralising the virus, leading to the loss of HBsAg[5].

Advances in direct-acting antiviral (DAA) regimens for chronic HCV infection (CHC) have achieved high rates of sustained virologic response (SVR)[6].

In HBV/HCV coinfected patients, HBV reactivation (HBVr) may occur during or after DAA therapy[7], typically 4-8 weeks after treatment initiation[8,9], and HBsAg loss occurs infrequently[10].

HBVr is defined as an abrupt increase in HBV replication in a patient with inactive (HBeAg-negative chronic infection) or resolved infection (HBsAg-negative, anti-HBc-positive)[11], due to natural or iatrogenic loss of HBV immune control. It may occur spontaneously, but is more frequent in patients with HIV, autoimmune disease, organ transplantation, or may be triggered by immunosuppressive therapy[8]. It is commonly defined by either the reappearance of HBV DNA (>100 IU/mL) or HBsAg (HBsAg seroreversion) in individuals with previously undetectable levels, or by at least a 10-fold increase in HBV DNA levels from baseline[12]. Clinical manifestations of

 — © 2026 The Author(s). CC BY 4.0

HBVr range from asymptomatic to symptomatic, including acute liver failure and death[11].

The European Association for the Study of the Liver[12] and the American Association for the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA)[6] recommend screening patients before DAA initiation for HBsAg, anti-HBc and anti-HBs, and if either HBsAg or anti-HBc are positive, adding serum HBV DNA levels.

Both European and American guidelines state that patients fulfilling the standard criteria for HBV treatment should receive NA therapy, during HCV treatment. EASL recommends: 1) all HBsAg-positive patients with chronic HCV infection should be treated with DAA; 2) all HBsAg-positive patients with cirrhosis (even if HBV DNA is undetectable) should receive NA therapy during anti-HCV DAA to prevent HBVr; and most recent guidelines[12] also state that 3) prophylactic NA treatment to prevent HBVr during anti-HCV DAA can be given in patients not meeting the indication for treatment of chronic HBV-monoinfection (e.g. HBV DNA <2000 IU/mL, normal ALT and absence of advanced fibrosis/cirrhosis) (weak recommendation). After initiation, EASL guidelines recommend continuing NA therapy for at least 12 weeks after HCV treatment[12].

Case Presentation

We report a 40-year-old woman with HBV/HCV coinfection, with a history of intravenous drug use. Her baseline laboratory results were: HBsAg-positive, anti-HBc-positive and anti-HBe-positive, HBV DNA undetectable, qHBsAg 33 IU/mL, normal alanine aminotransferase (ALT) levels, HCV RNA 1584000 IU/mL (genotype 1a). The transient elastography (TE) revealed 3.1 kPa. A 12-week course of grazoprevir/elbasvir was selected in accordance with the guidelines in effect at the time (2019). As HBV DNA was undetectable, active HBV monitoring was initiated.

After 4 weeks of DAA treatment, the laboratory results were: normal ALT levels, HCV RNA <15 IU/mL and HBV DNA 1410 IU/mL. At this point, HBV treatment was not started.

Table I. Consecutive laboratory findings regarding HBV, HCV, and liver aminotransferases

Parameters	Baseline	Week 4	Week 8	Week 12	Week 24	Week 48	Week 56	Week 82
HCV RNA, IU/mL	1584000	<15	UND	—	UND	UND	UND	UND
HBsAg	positive	positive	positive	—	—	positive	negative	negative
qHBsAg, IU/mL	33	—	—	—	—	—	—	—
HBeAg	negative	—	—	—	—	—	—	—
anti-HBc	positive	—	—	—	—	—	—	—
anti-HBe	positive	—	—	—	—	—	—	—
anti-HBs, IU/mL	negative	—	negative	—	—	negative	1.86	—
HBV DNA, IU/mL	UND	1410	60100	—	—	UND	UND	UND
AST, U/L	20	13	15	—	12	14	12	13
ALT, U/L	21	9	16	—	8	18	7	7

Results are presented at baseline (before DAA initiation) and 4, 8, 12, 24, 48, 56, and 82 weeks after DAA initiation. Abbreviations: ALT, alanine aminotransferase; anti-HBc, hepatitis B core antibody; anti-HBe, antibody to hepatitis B e antigen; anti-HBs, hepatitis B surface antibody; AST, aspartate aminotransferase; DAA, direct-acting antiviral; DNA, deoxyribonucleic acid; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; qHBsAg, quantitative hepatitis B surface antigen; RNA, ribonucleic acid; UND, undetectable; —, not assessed.

 — © 2026 The Author(s). CC BY 4.0

The laboratory results at week 8 showed undetectable HCV RNA but an increase of HBV DNA (60100 IU/mL), with normal liver function. At this stage, there were several unsuccessful attempts to contact the patient, and she was lost to follow-up, despite remaining DAA-compliant.

The patient returned for follow-up at week 24, and during this interval, there were no clinical manifestations reported by the patient. The laboratory results confirmed SVR for HCV and undetectable HBV DNA. At week 56, HCV RNA, HBV DNA and HBsAg were negative, with anti-HBs 1.86 IU/mL. After a two-year follow-up, the HBV/HCV status remained unchanged (Table I).

HBV reactivation occurred during DAA treatment (between weeks 4 and 8) without biochemical hepatitis, no clinical manifestations, with prior undetectable HBV DNA and very low qHBsAg. HBsAg loss occurred 56 weeks after starting DAA therapy.

Discussion

The risk of HBVr in HBsAg-positive patients ranges from 5.9% to 24.0%, while hepatitis flares are less frequent[12]. The different definitions of HBVr and the heterogeneity across studies are probably responsible for this disparity.

In HBV/HCV coinfection, virological patterns are dynamic, with one virus often suppressing the other[12]. Cross-sectional studies have shown that coinfected individuals often have high levels of HCV RNA, low or undetectable HBV DNA, and lower levels of HBsAg compared with HBV monoinfection[9]. Thus, HCV is most often the primary target of antiviral therapy. However, longitudinal studies have demonstrated that the levels of HBV DNA and HCV RNA may fluctuate with time, suggesting that competitive interactions between the two viruses are more dynamic than previously thought[9].

After hepatitis C treatment, HCV clearance can lead to HBVr, during or after DAA therapy[12].

Regarding HBV/HCV coinfection, and according to several meta-analyses, the overall risk during or after HCV treatment remains low, with reporting rates between 0.2% and 2.0%[7,13,14,15], and when HBV DNA rebound occurs, it is usually transient. One study reported HBVr in 10.0% of cases (8/79)[16], and criteria for HBVr were (1) HBV DNA was undetectable pre-DAA therapy and became detectable post-therapy, or (2) HBV DNA was detectable pre-treatment, but not quantifiable (< 20 IU/mL) and became quantifiable post-treatment. In this study when HBVr occurred, HBV DNA levels were low and transient, and not accompanied by HBsAg seroreversion or ALT elevation. They concluded that the risk of reactivation was low in CHC patients with resolved HBV during DAA therapy, and suggested testing for HBV DNA only in selected patients with ALT flares or failure of ALT normalisation during DAA treatment.

As mentioned in a meta-analysis[15], when stratified by baseline HBV DNA, the undetectable HBV DNA group showed a significantly lower risk of reactivation than the detectable HBV DNA group. Higher baseline HBsAg or HBV DNA levels increase HBVr risk[12], although HBV reactivation may occur in patients with undetectable or low levels of HBV DNA[9,10].

In a recent study, 38.0% of HBV/HCV-coinfected patients had HBV reactivation, and 10.1% experienced HBsAg seroclearance[17]. The patients with pre-treatment HBsAg <10 IU/mL had higher rates of HBsAg seroclearance and lower risk of reactivation, while patients with HBsAg levels >10 IU/mL had a 1-year HBV reactivation incidence of 42.9%[17]. This study included cirrhotic patients not receiving NA treatment, which increases the risk of reactivation. On the other hand, the majority (7/8) of coinfected patients who achieved HBsAg seroclearance had very low pre-treatment HBsAg levels (<10 IU/mL), likely indicating the natural course of HBV in these patients rather than being a direct result of DAA.

Our patient had undetectable HBV DNA, low qHBsAg and low levels of fibrosis, so NA ther-

 — © 2026 The Author(s). CC BY 4.0

apy was not started, in accordance with clinical guidelines at the time.

At week 56 after starting DAA therapy, with SVR, there was HBsAg loss, following the HBVr.

Had NA treatment been initiated in our patient, would the outcome have been the same?

No ALT flares were observed before or at the peak of HBV DNA levels, indicating that on-treatment ALT monitoring may not be enough to detect HBVr[18].

Rapid HCV clearance following DAA therapy has been shown to restore innate antiviral responses[19]. Investigations have suggested that this is the time when there is a major change in the hepatic immunological environment with a decline in interferon signalling genes and proinflammatory cytokines, which could favour enhanced HBV replication[20]. This restoration of innate immunity may impact HBsAg seroclearance and may explain the dynamic changes observed in HBV/HCV patients.

Hepatic flares can enhance immune activity and facilitate HBsAg seroclearance, but in the reported case, flares were not observed. However, the acute rise in HBV DNA levels may have played a role in the immune-mediated mechanism. Dynamic virological profiles may be observed, related to the intermittent activity of both viruses[5].

Conclusion

A careful longitudinal evaluation of HBV and HCV viraemia levels is mandatory for a proper therapeutic approach in HBV/HCV coinfected individuals.

Author Contributions

Cristina Valente and Ruben Carvalho: Conceptualisation; Methodology; Writing - Original Draft; Writing - Review & Editing.

Funding

No funding was received for this study.

Ethics Statement

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Written informed consent was obtained from the patient for publication of clinical details.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infection to cirrhosis and primary liver cancer worldwide. *J Hepatol.* 2006;45(4):529–538. https://doi.org/10.1016/j.jhep.2006.05.013
2. Caccamo G, Saffioti F, Raimondo G. Hepatitis B virus and hepatitis C virus dual infection. *World J Gastroenterol.* 2014;20(40):14559–14567. https://doi.org/10.3748/wjg.v20.i40.14559
3. Yuen MF, Wong DKH, Sablon E, Tse E, Ng IOL, Yuan HJ, et al. HBsAg seroclearance in chronic hepatitis B in the Chinese: virological, histological, and clinical aspects. *Hepatology.* 2004;39(6):1694–1701. https://doi.org/10.1002/hep.20240
4. Fattovich G. Natural history of hepatitis B. *J Hepatol.* 2003;39(Suppl 1):S50–S58. https://doi.org/10.1016/S0168-8278(03)00139-9
5. Ferrari C. HBV and the immune response. *Liver Int.* 2015;35:121-8. https://doi.org/10.1111/liv.12749
6. Bhattacharya D, Aronsohn A, Price J, Lo Re V; AASLD-IDSA HCV Guidance Panel. Hepatitis C guidance 2023 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. *Clin Infect Dis.* 2023;77(9):1335–1342. https://doi.org/10.1093/cid/ciad319
7. Mücke MM, Backus LI, Mücke VT, Coppola N, Preda CM, Yeh ML, et al. Hepatitis B virus reactivation during direct-acting antiviral therapy for hepatitis C: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol.* 2018;3(3):172–180. https://doi.org/10.1016/S2468-1253(18)30002-5
8. Bersoff-Matcha SJ, Cao K, Jason M, Ajao A, Jones SC, Meyer T, et al. Hepatitis B virus reactivation associated with direct-acting antiviral therapy for chronic hepatitis C virus: a review of cases reported to the U.S. Food and Drug Administration Adverse Event Reporting System. *Ann Intern Med.* 2017;166(11):792–798. https://doi.org/10.7326/M17-0377

 — © 2026 The Author(s). CC BY 4.0

9. Perrillo RP. Hepatitis B virus reactivation during direct-acting antiviral treatment of chronic hepatitis C: a hidden danger of an otherwise major success story. *Hepatology*. 2017;66(1):4–6. https://doi.org/10.1002/hep.29185

10. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67(4):1560–1599. https://doi.org/10.1002/hep.29800

11. Hoofnagle JH. Reactivation of hepatitis B. *Hepatology*. 2009;49(Suppl 5):S156–S165. https://doi.org/10.1002/hep.22945

12. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2025;83(2):502–583. https://doi.org/10.1016/j.jhep.2025.03.018

13. Chen G, Wang C, Chen J, Ji D, Wang Y, Wu V, et al. Hepatitis B reactivation in hepatitis B and C coinfected patients treated with antiviral agents: a systematic review and meta-analysis. *Hepatology*. 2017;66(1):13–26. https://doi.org/10.1002/hep.29109

14. Jaroszewicz J, Pawłowska M, Simon K, Zarębska-Michaluk D, Lorenc B, Klapaczyński J, et al. Low risk of HBV reactivation in a large European cohort of HCV/HBV coinfected patients treated with DAA. *Expert Rev Anti Infect Ther*. 2020;18(10):1045–1054. https://doi.org/10.1080/14787210.2020.1782189

15. Oh JH, Park DA, Ko MJ, Yoo JJ, Yim SY, Ahn JH, et al. Direct-acting antivirals and the risk of hepatitis B reactivation in hepatitis B and C coinfected patients: a systematic review and meta-analysis. *J Pers Med*. 2022;12(12):1957. https://doi.org/10.3390/jpm12121957

16. Majeed NA, Alawad AS, Liem KS, Takyar V, Alter H, Feld JJ, et al. Low rate of hepatitis B reactivation among patients with chronic hepatitis C during direct-acting antiviral therapy. *Dig Dis Sci*. 2023;68(8):3193–3198. https://doi.org/10.1007/s10620-023-07916-2

17. Yeh ML, Huang CF, Huang CI, Holmes JA, Hsieh MH, Tsai YS, et al. Hepatitis B-related outcomes following direct-acting antiviral therapy in Taiwanese patients with chronic HBV/HCV co-infection. *J Hepatol*. 2020;73(1):62–71. https://doi.org/10.1016/j.jhep.2020.01.027

18. Azeem HA, Alkabeer AM, Mohammed AS, Hussein A. Study of hepatitis B virus infection and reactivation among patients with chronic hepatitis C infection treated with direct antiviral agents. *Egypt Liver J*. 2021;11:88. https://doi.org/10.1186/s43066-021-00121-8

19. Serti E, Park H, Keane M, O'Keefe AC, Rivera E, Liang TJ, et al. Rapid decrease in hepatitis C viremia by direct-acting antiviral therapy improves the natural killer cell response to IFNα. *Gut*. 2017;66(4):724–735. https://doi.org/10.1136/gutjnl-2015-310033

20. Meissner EG, Wu D, Osinusi A, Bon D, Virtaneva K, Sturdevant D, et al. Endogenous intrahepatic IFNs and association with IFN-free HCV treatment outcome. *J Clin Invest*. 2014;124(8):3352–3363. https://doi.org/10.1172/JCI75938

 — © 2026 The Author(s). CC BY 4.0