Liver Research 3 (2019) 75–79

Contents lists available at ScienceDirect

Liver Research

journal homepage: http://www.keaipublishing.com/en/journals/liver-research

Review Article

Risk assessment and management of hepatitis B reactivation from direct-acting antivirals for hepatitis C☆

Maureen Whitsett, David M. Feldman, Calvin Q. Pan*

Division of Gastroenterology and Hepatology, Department of Medicine, NYU Langone Health, New York University School of Medicine, New York, NY, USA

ARTICLE INFO

Article history:
Received 26 September 2018
Received in revised form
22 November 2018
Accepted 14 March 2019

Keywords:
Co-infection
Treatment induced flares
Hepatitis B exacerbation
Hepatitis C therapy
Prevention of disease reactivation

ABSTRACT

Although hepatitis B virus (HBV) reactivation has been reported in hepatitis C patients who received interferon therapy, rare cases of HBV reactivation occur in the context of direct-acting antiviral (DAA) agent therapy for treatment of hepatitis C virus (HCV) infection. Recent studies observed that the reactivations were predominantly in hepatitis B surface antigen (HBsAg) positive patients, but reactivation can rarely occur in patients who are HBsAg negative and hepatitis B core antibody (HBcAb) positive. The severity of an HBV flare varies. In some cases, severe liver injury or fulminant hepatic failure may occur. HBV reactivation may occur regardless of HCV genotype and type of DAA regimens. The onset of HBV reactivation can range from 4 to 48 weeks after initiating DAA therapy. These patients may have undetectable levels of HBV deoxyribonucleic acid (DNA) prior to DAA treatment. Pre-emptive antiviral therapy for HBV should be considered in HBsAg-positive patients with high levels of viremia who are not receiving HBV treatment. If HBV DNA viral load is less than the guideline criteria for HBV treatment, one should consider pre-emptive HBV antiviral versus HBV DNA monitoring during DAA therapy. For patients who are HBsAg negative but HBcAb positive, close monitoring of serum alanine aminotransferase (ALT) levels during/post-treatment is highly recommended. The current review summarizes the recommendations of different society guidelines and discusses the appropriate management strategies in various patient profiles.

1. Introduction

Co-infection with hepatitis C virus (HCV) and hepatitis B virus (HBV) represents a significant challenge to health care providers, as patients with co-infection and HBV viremia tend to develop liver fibrosis and hepatocellular carcinoma at higher rates than those with mono-infection.[1] Co-infection of HCV and HBV, which share routes of transmission, can be observed in high-risk patient populations, organ transplant recipients, as well as those living in endemic areas.[2] In 2016, the global prevalence of chronic HBV infection was estimated to be nearly 4%.[3] Over 71 million people, or 1% of the global population, are estimated to have HCV infection.[4] In addition, among 350 million carriers of HBV in the world, it is estimated that approximately 3.5–7 million patients are co-infected with HCV.[5]

Guidelines for the treatment of HCV and HBV offer similar parameters for when to offer treatment;[6] however, recommendations on the management of co-infected patients vary among different societies. The American Association for the Study of Liver Disease (AASLD) and European Association for the Study of the Liver (EASL) recommend treatment initiation for all patients with HCV infection, regardless of the presence or absence of cirrhosis. Both organizations offer treatment regimen suggestions for direct-acting antiviral (DAA) therapy with or without ribavirin or interferon.[7,8] The recommendation to initiate treatment of HBV depends upon the viremia levels, elevation of alanine aminotransferase (ALT), as well as the presence of fibrosis. Treatment of HBV is also indicated in special patient populations, such as patients who have active HBV infection and are undergoing chemotherapy or pregnant mothers with high levels of HBV deoxyribonucleic acid (DNA) during late pregnancy.[9,10] Patients with chronic HBV who are not receiving treatment require monitoring at regular intervals.[11,12] Hepatitis B reactivation is defined as an abrupt increase in the HBV and is well-documented in patients with previously undetected HBV DNA due to inactive or resolved HBV infection.[13]

☆ Edited by Peiling Zhu and Genshu Wang.

* Corresponding author.
E-mail address: Panc01@NYU.edu (C.Q. Pan).

https://doi.org/10.1016/j.livres.2019.03.002

While HBV reactivation was a known phenomenon with interferon-based therapy for patients with HBV and HCV co-infection,[14–17] the surge of numbers of HBV reactivation cases in co-infected patients had not been reported until after Food and Drug Administration (FDA) approval of DAA treatment in HCV patients.[18] In a recent report from FDA, among 29 patients who received DAA therapy and presented with HBV reactivation, one patient required a liver transplant and one patient died from acute liver failure. The post-marketing DAA safety report prompted the FDA to release a black box warning which required that physicians screen for co-infection of HBV in all patients who will begin DAA therapy. In addition, close monitoring of co-infected patients for reactivation is mandated by society guidelines.[19] The current review will provide the updates on the data relevant to the risk assessment of HBV reactivation in HCV patients on DAA therapy. We also summarize the recommendations of the society guidelines and discuss the appropriate management strategies in different patient profiles.

2. Patients' profile from case reports and case series

Prior to the release of a black box warning for hepatitis B reactivation by the FDA on DAA therapy, there were five case reports and an observational study by Wang *et al.* which describe HBV reactivation in DAA treated HCV patients with HBV co-infection.[20–26] These case reports and clinical observations indicated that reactivation can be transient and without clinical symptoms. However, it usually causes a hepatitis flare. HBV reactivation may occur regardless of HCV genotype and type of DAA regimens, regardless of baseline HBV DNA levels and even in patients with undetectable levels pre-treatment, and can occur anywhere from 4 to 48 weeks after initiation of therapy.[27–29] Two case reports have detailed reactivation in 3 patients since the FDA released its black box warning.[7,30] The patients' profiles and their baseline risk for HBV reactivation are presented in Table 1[7,20–25,30].

In addition to case reports, two observational case series have been published recently. Wang *et al.*[26] conducted an observational study in China in 2016 and observed that the severity of HBV reactivation was associated with HBsAg status. Among ten HBsAg-positive patients who underwent DAA therapy, 3/10 (30%) of them presented with HBV reactivation after initiating DAA treatment. The outcomes of these patients were the following: one had an asymptomatic reactivation, one developed clinically apparent jaundice, and one developed "hepatic failure". None of the 124 HBsAg negative patients (0%) who were considered having occult HBV infection had HBV reactivation during or post DAA treatment.[26] All patients developed HBsAg positivity with DAA therapy although it is unclear when the HBsAg seroreversion (HBV serological reactivation) occurred. In 2017, Bersoff-Matcha *et al.*[19] reported 29 cases of HBV reactivation in an FDA review of the safety of DAAs. Ten of the patients do not have any laboratory data (prior to starting DAA therapy). Nine patients had detectable HBV DNA prior to starting therapy, 7 patients were positive for HBsAg with undetectable HBV DNA, and 3 patients had no detectable HBV DNA and negative HBsAg. Mean age for individuals as 60.7 years, 13 were men, 16 were women. 16 patients had genotype 1, 2 with other genotypes, and 11 with unclear genotypes. Time to reactivation ranged from 14 days to 196 days. There were 2 deaths and one patient required liver transplantation.[19] These studies demonstrate that patients who are HBsAg negative can indeed develop HBV reaction, albeit the frequency of reactivation is quite low.

3. Risk analyses of HBV reactivation in cohort studies

The risk of HBV reactivation in HCV infected patients was also analyzed in several retrospective and prospective cohort studies.[31,32] Using the electronically retrieved cohort of HCV infected veterans (ERCHIVES) database, Butt *et al.*[33] examined 34 632 patients who received DAA therapy for HCV. HBV reactivation was defined variably in this cohort of patients. In this group, the rate of HBV reactivation was 2.4% ($P < 0.001$, lower than the 17.7% rate observed in the peg-interferon/ribavirin arm). Of the larger treatment group, 33.9% of patients were HBcAb+ (9343/27 550), 11.1% of patients were HBsAg+ (3322/29 886), and 4.4% of patients were HBeAg+ (84/1898).

Table 1
Overview of clinical characteristics and risk factors in HCV patient cases with HBV reactivation after initiating DAA treatment.

References	Age (year)	Gender	HCV genotype	HBV status	DAA regimen	Reactivation time	HBV reactivation	Clinical outcomes
Collins *et al.*[20]	55	M	1a	HBV DNA 2300 IU/mL, HBeAb+	Sofosbuvir, simeprevir	7–8 weeks	HBV viremia, ALT/INR elevation	Acute liver injury
Collins *et al.*[20]	57	M	1a	HBcAb+, HBsAg/Ab-, viral load <20 IU/mL	Sofosbuvir, simeprevir	2–3 weeks	HBV viremia	Asymptomatic viremia
Ende *et al.*[22]	59	W	1b	HBsAg-, HBsAb-, HBcAb+, HBV DNA undetectable	Simeprevir, sofosbuvir, ribavirin	11 weeks	HBV viremia, HBsAg+, ALT/INR elevation	Acute liver failure, liver transplantation
De Monte *et al.*[a,21]	53	M	4d	HBcAb+, HBeAb+, HBeAg-, HBsAg/Ab-	Ledipasvir, sofosbuvir	13 weeks	HBV viremia, HBsAg+, ALT increase	
Hayashi *et al.*[23]	83	W	1b	HBsAg-	Daclatasvir, asunaprevir	>24 weeks	HBV viremia, HBsAg+, (found to be HBcAb+), ALT/INR increase	Acute liver failure, no transplant
Takayama *et al.*[25]	69	M	1b	HBcAb+, HBV 2.5 log copies/mL, HBeAg-	Daclatasvir, asunaprevir	43 days	HBV viremia, ALT elevation	Asymptomatic hepatitis
Madonia *et al.*[b,24]	62	W	2	HBcAb+, HBsAg/Ab-, HBV DNA undetectable	Sofosbuvir, ribavirin	7 months	HBV viremia, HBsAg+, HBeAg+, ALT elevation	Symptomatic acute hepatitis
Tucci *et al.*[7]	57	M	1b	HBcAb+, HBV DNA undetectable	Sofosbuvir, ledipasvir, ribavirin	16 months	HBV viremia, HBsAg+, ALT elevation	Acute hepatitis
Pol *et al.*[30]	51	W	2	HBcAb+, HBV DNA<10 IU/mL	Sofosbuvir, ribavirin	2 months	HBV viremia, HBsAg+, ALT elevation	Acute hepatitis
Pol *et al.*[30]	65	M	4	HBcAb+, HBsAg-, HBV DNA undetectable	Sofosbuvir, ledipasvir	7 months	HBsAg+	Acute hepatitis

[a] Human immunodeficiency virus (HIV) co-infection, on anti-retroviral therapy.
[b] Received chemotherapy prior to DAA therapy.
Abbreviations: M, man; W, woman; DAA, direct-acting antiviral; ALT, alanine aminotransferase; DNA, deoxyribonucleic acid; HBV, hepatitis B virus; HBcAb, hepatitis B core antibody; HBeAg, hepatitis B e antigen; HBeAb, hepatitis B e antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; INR, international normalized ratio.

Liu *et al.*[5] performed a prospective, phase 3b, multicenter, open-label study which entailed treatment of HBV/HCV co-infected patients with sofosbuvir and ledipasvir for 12 weeks. There were 111 total patients. Only 5 patients experienced an increased HBV DNA and ALT elevation >2 times the upper limit of normal (ULN) during treatment. Only one of these patients developed symptomatic acute hepatitis with HBV reactivation. There were 70 patients with HBV DNA levels of 20 IU/mL prior to starting treatment; 53% of these patients experienced an increase in HBV DNA of at least 1 log10 during the 12 weeks of treatment. Serper *et al.*[34] examined the rate of significant ALT flares, HBV reactivation, and hepatic decompensation in patients with positive HBcAb who received DAA therapy within the Veterans Affairs healthcare system. In total, during treatment, 14% of patients developed ALT elevation greater than or equal to 2 times the ULN, 3% of patients developed elevations 4 times the ULN, 20 patients had ALT elevations exceeding 300 IU/mL, and 2 patients had ALT elevations exceeding 1000 IU/mL.

Tamori *et al.*'s study aimed to compare the rate of HBV reactivation in those with "resolved HBV infection" ($N = 765$), defined as HBcAb+, and those with co-infection ($N = 25$), defined as HBsAg+. HBV reactivation was defined as either new HBV viremia >20 IU/mL or an increase in the viral load greater than 2 log copies/mL. Following EASL recommendation for HBV/HCV co-infection and DAA therapy, three patients in the HBsAg+ group with HBV DNA >2000 IU/mL before treatment were started on entecavir prior to DAA therapy. Throughout treatment and afterwards their viral loads remained undetectable 12 weeks after completion of DAA therapy. Three patients in the same group with HBV DNA <2000 IU/mL experienced HBV reactivation during DAA therapy. Only one patient of 765 in the resolved HBV infection group experienced HBV reactivation, which was an appearance of HBV viral DNA of 21 IU/mL. This study seems to support that very rarely patients with HBcAb will reactivate when treated with DAA therapy.[35]

4. Current recommendations from guidelines

Current major guidelines strongly recommend screening for HBV infection for any patient with HCV before initiation and during DAA therapy regardless of past HBV status, HCV genotype and class of DAAs used. HBV reactivation can be prevented with pre-DAA-treatment screening and prophylactic treatment when necessary. The FDA guidelines recommend periodic monitoring for reactivation in patients with prior HBV exposure (or HBcAb+, HBsAg-) in addition to those with chronic infection (HBsAg+, HBcAb-).[19] Both EASL and AASLD make suggestions regarding appropriate candidates for HBV therapy with DAA treatment. The AASLD recommends treatment of any patient who would normally meet criteria for HBV therapy (for HBeAg-negative patients with HBV DNA >2000 IU/mL) as well as any patient with coinfection and cirrhosis. For patients who are HBcAb+ but HBsAg- (thus patients who would not qualify for nucleo(t)side treatment), ALT should be assessed at the start and completion of treatment as well as at varying intervals post-treatment. HBV DNA and HBsAg should be tested if ALT increases or fails to normalize after treatment. Treatment options for co-infected patients include entecavir or tenofovir (TDF or TAF). Additionally, any patient with risk factors for HBV acquisition receiving DAA therapy should receive HBV vaccination.[11] EASL recommendations vary in the suggestion that those with HBsAg+ should receive nucleo(t)side prophylaxis for 12 weeks post-treatment with DAA.[12] Neither organization recommends testing for HBV DNA at the initiation of DAA treatment routinely to identify patients with occult HBV infection. The summary of the aforementioned guidelines is presented in Table 2.

5. Discussions

There are numerous postulated mechanisms for HBV reactivation during treatment, many of which are based upon clinical observations. HCV infection tends to predominate in many co-infected patients, which suggests that HBV viral replication is somehow suppressed by active HCV infection. One possible mechanism is that HCV viremia induces expression of certain interferons which suppress HBV;[36] clinically, this seems to be supported by the fact that patients who have received interferon-based therapies experience HBV reactivation once therapy has completed. As DAA therapy typically leads to a rapid reduction in HCV levels within weeks,[37] HBV reactivation has been observed much earlier in those treated with DAA compared to interferon-based regimens.[38] The risk of reactivation of HBV in immunocompromised patients has been well-described, as lymphocyte depletion and poor antibody production permits unchecked HBV replication as well as protein expression. Fatality rates are reported as high as 10% in certain cancer patient populations.[5] The risk of reactivation with serious clinical consequences in patients undergoing DAA therapy is still unclear, though present studies suggest it is lower in those without HBsAg expression when compared to those with chronic HBV.[39,40] A recent meta-analysis by Mücke *et al.*[38] noted that within the available literature, no cases of HBV-related hepatitis were reported in patients with HBV reactivation with resolved infection (anti-HBc+ but HBsAg-).

As more data are required to evaluate the underlying mechanisms of HBV reactivation in this setting, it remains unclear which patients should receive prophylaxis with DAA therapy (beyond those eligible for HBV treatment) as well as if HBV DNA should be checked at least once in all patients. It is recommended that prior to initiating therapy with DAA patients undergo testing for the presence of HBsAg as well as anti-HBc. Additionally, it is important to understand that a baseline HBV DNA level should be obtained as this would allow for detection of reactivation based upon the increase in HBV DNA by greater than 1 log copies/mL.[5] Patients with cirrhosis, irrespective of the presence of HBsAg, should undergo treatment for HBV concurrently. Additionally, those who meet

Table 2
Current recommendations from guidelines on the screening and pre-emptive treatment of HBV in patients with HCV prior to DAA therapy.

Treatment	AASLD[a] (2017)	EASL[b] (2016)	US FDA[c]
Screening for HBV serology	Must	Must	Must
Preemptive antiviral therapy for HBV	All HBsAg+ or monitor patients, treat if HBV DNA >10-fold of baseline or to >1000 IU/mL	All HBsAg+ or HBsAg- occult HBV infection	Consult hepatologist
Monitoring	Yes	Yes	Yes

[a] AASLD/ISDA. HCV guidance: Recommendations for testing, managing, and treating hepatitis C. Updated September 2017.
[b] EASL recommendations on treatment of hepatitis C 2016. Journal of Hepatology.
[c] The US FDA. FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with DAAs for hepatitis C. 2016 [Nov 2016]. http://www.fda.gov/Drugs/DrugSafety/ucm522932.htm.
Abbreviations: AASLD, American Association for the Study of Liver Diseases; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; DNA, deoxyribonucleic acid; EASL, European Association for the Study of the Liver; FDA, Food and Drug Administration; US, the United States.

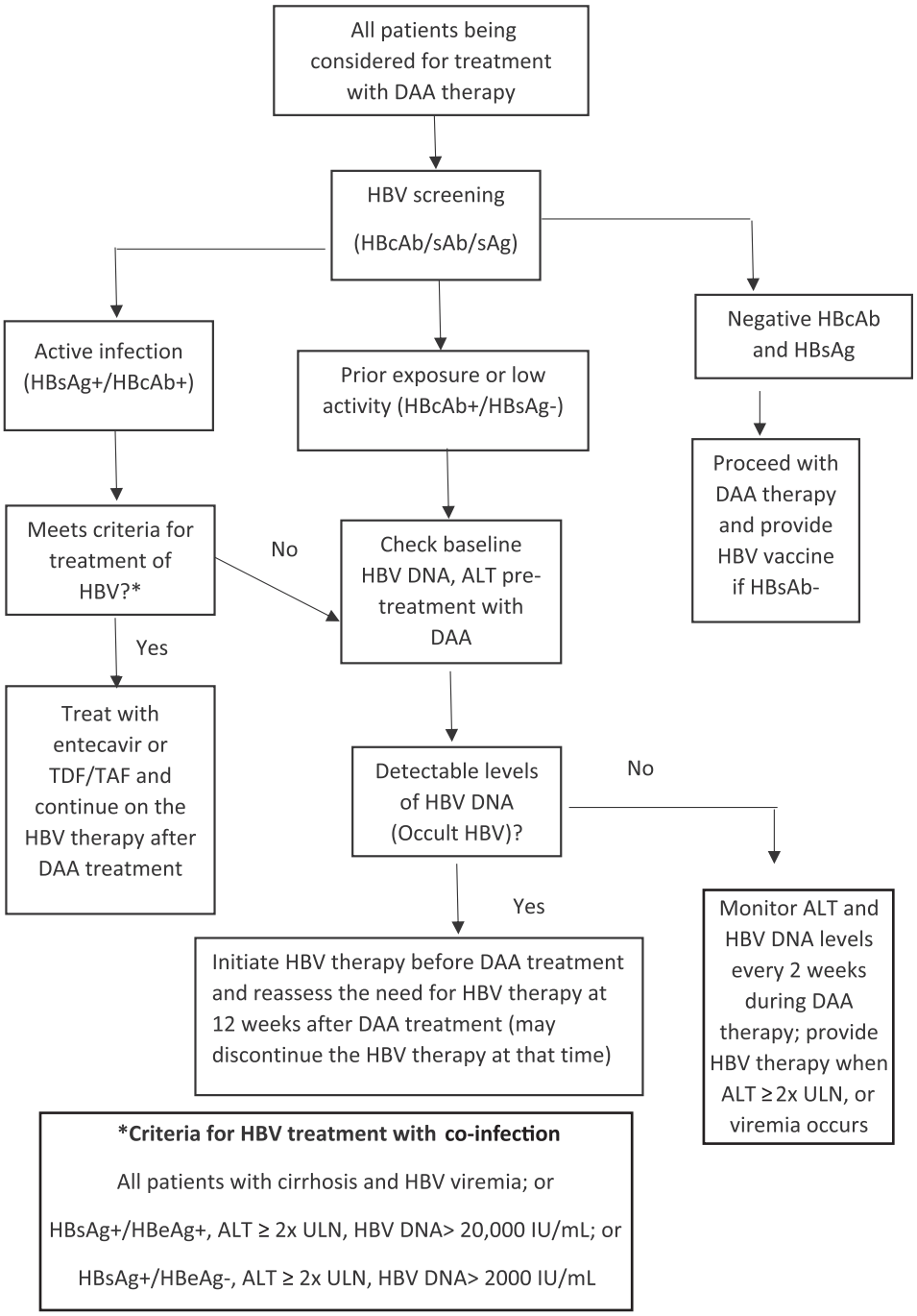

Fig. 1. Algorithm of managing patients with risk of hepatitis B reactivation from DAAs for hepatitis C. Abbreviations: DAA, direct-acting antiviral; ALT, alanine aminotransferase; DNA, deoxyribonucleic acid; HBV, hepatitis B virus; HBcAb, hepatitis B core antibody; HBeAg, hepatitis B e antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; ULN, upper limit of normal; TDF/TAF, tenofovir.

criteria for treatment under current AASLD guidelines should also receive therapy. It is reasonable to check both HBV DNA and HBsAg when ALT levels increase during treatment or after treatment and if ALT levels do not return to normal with HCV eradication. Finally, Serper *et al.*'s suggestions are reasonable in terms of testing for the presence of HBsAg once sustained virologic response has been achieved in order to detect any subclinical seroconversion which arose with HCV eradication.[34]

In conclusions, rare cases of HBV reactivation occur in the context of HCV DAA therapy. Published data indicated that the reactivations were predominantly in HBsAg-positive patients, but they can rarely occur in patients who are HBsAg negative with HBcAb positivity. The severity of the flares has been highlighted by the FDA report, which presented 29 cases of HBV reactivation between 2013 and 2016 including 8 cases of fulminant hepatitis/liver failure, 2 deaths, and 1 required transplant. All major guidelines recommend that all patients initiating DAA therapy should undergo HBV testing prior to treatment. We proposed the clinical management algorithm of patients with risk of hepatitis B reactivation from DAAs for hepatitis C and presented it in Fig. 1. The pre-emptive

antiviral therapy for HBV should be considered in HBsAg-positive patients with high levels of viremia not already on HBV treatment. If HBV DNA is less than guideline criteria for HBV treatment, one should consider pre-emptive HBV antiviral therapy versus HBV DNA monitoring during DAA therapy. For patients who are HBsAg negative but HBcAb positive, there is insufficient evidence for firm guidelines on recommending pre-emptive HBV therapy. Therefore, close monitoring of serum ALT levels during/post-treatment (peak incidence of HBV reactivation at week 8–12 on-treatment, cases as late as 5 months post-treatment reported) is highly recommended.

Authors' contributions

C. Q. Pan provided concepts, outlines, and performed literature research. M. Whitsett also performed literature research. C. Q. Pan and M. Whitsett wrote the manuscript with assistance from D. M. Feldman. C. Q. Pan provided critical reviews and communicated with the journal.

Conflict of interest

C. Q. Pan has received research grants from Gilead and Merck. He also serves as a consultant or advisor for Gilead, and speakers' bureau for Gilead, Abbvie, and Intercept. Other authors have no conflicts of interest to disclosed.

Acknowledgements

The manuscript was prepared by authors without other assistance. We would like to thank Ms. Dan Wang for editorial works.

References

1. Kruse RL, Kramer JR, Tyson GL, et al. Clinical outcomes of hepatitis B virus coinfection in a United States cohort of hepatitis C virus-infected patients. *Hepatology*. 2014;60:1871–1878.
2. Chen G, Wang C, Chen J, et al. Hepatitis B reactivation in hepatitis B and C coinfected patients treated with antiviral agents: a systematic review and meta-analysis. *Hepatology*. 2017;66:13–26.
3. Ginzberg D, Wong RJ, Gish R. Global HBV burden: guesstimates and facts. *Hepatol Int*. 2018;12:315–329.
4. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol*. 2017;2:161–176.
5. Liu CJ, Chuang WL, Sheen IS, et al. Efficacy of ledipasvir and sofosbuvir treatment of HCV infection in patients coinfected with HBV. *Gastroenterology*. 2018;154:989–997.
6. Tong MJ, Pan CQ. An expert consensus for the management of chronic hepatitis B in Asian Americans. *Aliment Pharmacol Ther*. 2018;47:1181–1200.
7. Tucci A, Rizza S, Cocchis D, Martini S, Romagnoli R, Marzano A. Early and late hepatitis B reactivation after IFN- or DAA-based therapy of recurrent hepatitis C in anti-HBc-positive liver transplant recipients. *Transplantation*. 2018;102:e354–e355.
8. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology*. 2015;62:932–954.
9. Di Bisceglie AM, Lok AS, Martin P, Terrault N, Perrillo RP, Hoofnagle JH. Recent US Food and Drug Administration warnings on hepatitis B reactivation with immune-suppressing and anticancer drugs: just the tip of the iceberg? *Hepatology*. 2015;61:703–711.
10. Pan CQ, Duan Z, Dai E, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. *N Engl J Med*. 2016;374:2324–2334.
11. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67:1560–1599.
12. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67:370–398.
13. Calvaruso V, Ferraro D, Licata A, et al. HBV reactivation in patients with HCV/HBV cirrhosis on treatment with direct-acting antivirals. *J Viral Hepat*. 2018;25:72–79.
14. Kawagishi N, Suda G, Onozawa M, et al. Comparing the risk of hepatitis B virus reactivation between direct-acting antiviral therapies and interferon-based therapies for hepatitis C. *J Viral Hepat*. 2017;24:1098–1106.
15. Liaw YF, Chien RN, Lin SM, et al. Response of patients with dual hepatitis B virus and C virus infection to interferon therapy. *J Interferon Cytokine Res*. 1997;17:449–452.
16. Saitta C, Pontisso P, Brunetto MR, et al. Virological profiles in hepatitis B virus/hepatitis C virus coinfected patients under interferon plus ribavirin therapy. *Antivir Ther*. 2006;11:931–934.
17. Liu J. Hepatitis B reactivation in chronic hepatitis C patients treated with interferon or pan-oral direct-acting antivirals. *Hepatology*. 2018;67:453–454.
18. Pockros PJ. Black box warning for possible HBV reactivation during DAA therapy for chronic HCV infection. *Gastroenterol Hepatol (N Y)*. 2017;13:536–540.
19. Bersoff-Matcha SJ, Cao K, Jason M, 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;166:792–798.
20. Collins JM, Raphael KL, Terry C, et al. Hepatitis B virus reactivation during successful treatment of hepatitis C virus with sofosbuvir and simeprevir. *Clin Infect Dis*. 2015;61:1304–1306.
21. De Monte A, Courjon J, Anty R, et al. Direct-acting antiviral treatment in adults infected with hepatitis C virus: reactivation of hepatitis B virus coinfection as a further challenge. *J Clin Virol*. 2016;78:27–30.
22. Ende AR, Kim NH, Yeh MM, Harper J, Landis CS. Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: a case report. *J Med Case Rep*. 2015;9:164.
23. Hayashi K, Ishigami M, Ishizu Y, et al. A case of acute hepatitis B in a chronic hepatitis C patient after daclatasvir and asunaprevir combination therapy: hepatitis B virus reactivation or acute self-limited hepatitis? *Clin J Gastroenterol*. 2016;9:252–256.
24. Madonia S, Orlando E, Madonia G, Cannizzaro M. HCV/HBV coinfection: the dark side of DAAs treatment? *Liver Int*. 2017;37:1086–1087.
25. Takayama H, Sato T, Ikeda F, Fujiki S. Reactivation of hepatitis B virus during interferon-free therapy with daclatasvir and asunaprevir in patient with hepatitis B virus/hepatitis C virus co-infection. *Hepatol Res*. 2016;46:489–491.
26. Wang C, Ji D, Chen J, et al. Hepatitis due to reactivation of hepatitis B virus in endemic areas among patients with hepatitis C treated with direct-acting antiviral agents. *Clin Gastroenterol Hepatol*. 2017;15:132–136.
27. Doi A, Sakamori R, Tahata Y, et al. Frequency of, and factors associated with, hepatitis B virus reactivation in hepatitis C patients treated with all-oral direct-acting antivirals: analysis of a Japanese prospective cohort. *Hepatol Res*. 2017;47:1438–1444.
28. Loggi E, Gitto S, Galli S, et al. Hepatitis B virus reactivation among hepatitis C patients treated with direct-acting antiviral therapies in routine clinical practice. *J Clin Virol*. 2017;93:66–70.
29. Ogawa E, Furusyo N, Murata M, Toyoda K, Hayashi T, Ura K. Potential risk of HBV reactivation in patients with resolved HBV infection undergoing direct-acting antiviral treatment for HCV. *Liver Int*. 2018;38:76–83.
30. Pol S, Marion O, Vallet-Pichard A, et al. Direct-acting antivirals and hepatitis B virus (HBV) reactivation in co-infected HBV/HCV kidney-transplant recipients. *Transpl Infect Dis*. 2018;20:e12864.
31. Belperio PS, Shahoumian TA, Mole LA, Backus LI. Evaluation of hepatitis B reactivation among 62,920 veterans treated with oral hepatitis C antivirals. *Hepatology*. 2017;66:27–36.
32. Mücke VT, Mücke MM, Peiffer KH, et al. No evidence of hepatitis B virus reactivation in patients with resolved infection treated with direct-acting antivirals for hepatitis C in a large real-world cohort. *Aliment Pharmacol Ther*. 2017;46:432–439.
33. Butt AA, Yan P, Shaikh OS, Abou-Samra AB. Hepatitis B reactivation and outcomes in persons treated with directly acting antiviral agents against hepatitis C virus: results from ERCHIVES. *Aliment Pharmacol Ther*. 2018;47:412–420.
34. Serper M, Forde KA, Kaplan DE. Rare clinically significant hepatic events and hepatitis B reactivation occur more frequently following rather than during direct-acting antiviral therapy for chronic hepatitis C: data from a national US cohort. *J Viral Hepat*. 2018;25:187–197.
35. Tamori A, Abiru S, Enomoto H, et al. Low incidence of hepatitis B virus reactivation and subsequent hepatitis in patients with chronic hepatitis C receiving direct-acting antiviral therapy. *J Viral Hepat*. 2018;25:608–611.
36. Eyre NS, Phillips RJ, Bowden S, et al. Hepatitis B virus and hepatitis C virus interaction in Huh-7 cells. *J Hepatol*. 2009;51:446–457.
37. Pan CQ, Tiongson BC, Hu KQ, et al. Real-world study on sofosbuvir-based therapies in Asian Americans with chronic hepatitis C. *J Clin Gastroenterol*. 2019;53:147–154.
38. Mücke MM, Backus LI, Mücke VT, et al. Hepatitis B virus reactivation during direct-acting antiviral therapy for hepatitis C: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2018;3:172–180.
39. Sulkowski MS, Chuang WL, Kao JH, et al. No evidence of reactivation of hepatitis B virus among patients treated with ledipasvir-sofosbuvir for hepatitis C virus infection. *Clin Infect Dis*. 2016;63:1202–1204.
40. Tang L, Tolaymat M, Stonesifer E, Kottilil S, Wilson E. Absence of hepatitis B reactivation among veterans with serological evidence of previous hepatitis B infection receiving anti-hepatitis C direct acting antivirals. *J Hepatol*. 2017;66:S251–S252.