Cessation of Nucleoside/Nucleotide Analogue Therapy in Chronic Hepatitis B HBeAg-Negative Patients

Paul J. Pockros, MD,[1,2] and Ashwini Mulgaonkar, MD[1]

[1]Division of Gastroenterology/Hepatology, Scripps Clinic, La Jolla, California

[2]Department of Immunology and Microbiology, The Scripps Research Institute, La Jolla, California

Corresponding author:
Dr Paul J. Pockros
Division of Gastroenterology/Hepatology
Scripps Clinic
10666 N. Torrey Pines Road
La Jolla, CA 92037
Tel: (858) 554-8879
Fax: (858) 554-8065
E-mail: pockros.paul@scrippshealth.org

Abstract: Most patients treated for chronic hepatitis B infection require lifelong treatment with nucleoside/nucleotide analogues (NAs), which inhibit hepatitis B virus (HBV) replication but do not eradicate the virus or achieve a functional cure. Withdrawal of NA treatment is being considered as a path to functional cure by provoking HBV reactivation, followed by immune consolidation and subsequent hepatitis B surface antigen loss in some patients. However, in rare cases, NA therapy withdrawal causes severe hepatitis flares, hepatic decompensation, or death, and predictors of hepatic decompensation or death with NA withdrawal have not been well established. This article reviews the current standard of care for HBV and the results of recent trials that clarify the safety of NA treatment cessation relative to the benefit of functional cure.

Keywords
Nucleoside analogues, nucleotide analogues, chronic hepatitis B, functional cure, relapse, hepatic decompensation, acute liver failure

Chronic hepatitis B (CHB) infection is a challenging public health issue that is currently incurable. Most patients are untreated, and those who are treated usually require lifelong therapy with nucleoside/nucleotide analogues (NAs), which inhibit hepatitis B virus (HBV) replication but do not eradicate the virus.[1,2]

Current American Association for the Study of Liver Diseases (AASLD) guidelines published initially in 2016 and updated in 2018 note that CHB therapy should be started in patients with immune-active CHB and alanine aminotransferase (ALT) levels at least twice the upper limit of normal (with the upper limit of normal being 35 U/L in males and 25 U/L in females) and who are either hepatitis B envelope antigen (HBeAg)-positive or -negative.[3] To begin treatment, HBV DNA should be greater than 20,000 IU/mL if the patient is HBeAg-positive, and HBV DNA should be greater than or equal to 2000 IU/mL if the patient is HBeAg-negative (Figure 1). Therapy is also recommended for patients with immune-active CHB with cirrhosis and an HBV DNA greater than 2000 IU/mL, regardless of ALT level.

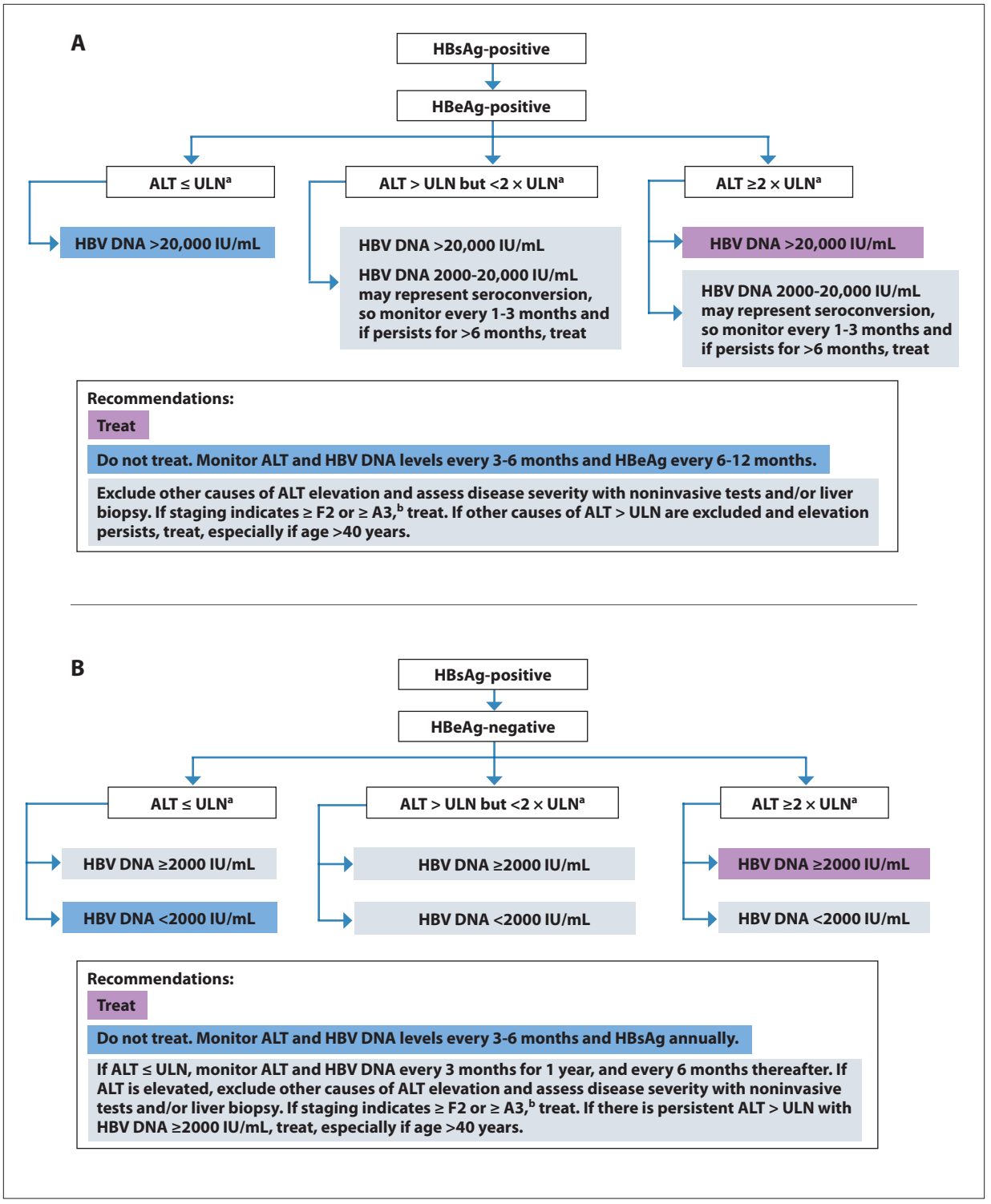

Figure 1. Algorithm from the 2018 American Association for the Study of Liver Diseases guidelines for management of HBsAg-positive patients without cirrhosis who are HBeAg-positive (**A**) or HBeAg-negative (**B**). Adapted from Terrault et al.[3]

ALT, alanine aminotransferase; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ULN, upper limit of normal.

[a]The ULNs for ALT in healthy adults are reported to be 29-33 U/L for males and 19-25 U/L for females. The recommended ULN for ALT to guide management decisions is 35 U/L for males and 25 U/L for females.

[b]F2 signifies stage 2 fibrosis and A3 signifies stage 3 inflammation.

Duration of Therapy

The duration of therapy is variable and is influenced by HBeAg status, duration of HBV DNA suppression, and presence of cirrhosis. Guidelines suggest that CHB HBeAg-positive adults without cirrhosis who seroconvert to CHB HBeAg-negative and anti–hepatitis B envelope antibody (HBeAb)-positive while on therapy can discontinue NAs after a 12-month duration of treatment consolidation (as long as they have normal ALT and undetectable HBV DNA).[3] Treatment discontinuation requires consideration of risk for virologic relapse, decompensation, liver cancer, or death, and the burden of continued antiviral therapy. Whether a longer duration of consolidation reduces rates of virologic relapse is currently unclear.

Guidelines suggest indefinite antiviral therapy in CHB HBeAg-positive adults with cirrhosis, regardless of HBV DNA level, HBeAg status, or ALT level, to decrease the risk of worsening liver-related complications. The AASLD also suggests, with low quality and certainty of evidence and a conditional recommendation, indefinite antiviral therapy for adults with HBeAg-negative, immune-active CHB without a compelling reason for withdrawing treatment. The AASLD further states that a decision to stop therapy for adult patients who are HBeAg-negative and do not have cirrhosis must take into account the risk of virologic relapse, decompensation, financial burden of continued treatment, and preferences of the patient and provider. This population represents the majority of HBV-infected patients in the United States.

Functional Cure of Chronic Hepatitis B

A functional cure, defined as loss of hepatitis B surface antigen (HBsAg) with or without seroconversion of hepatitis B surface antibody (HBsAb), has been considered a surrogate endpoint of treatment but is rarely achieved with NAs.[3,4] Withdrawal of NA treatment is being considered as a path to functional cure by provoking HBV reactivation, followed by immune consolidation and subsequent HBsAg loss in some patients.[2,4,5] However, in rare cases, NA therapy withdrawal causes severe hepatitis flares, hepatic decompensation, or death. Predictors of hepatic decompensation or death with NA withdrawal have not been well established.[4]

Current guidelines from the European Association for the Study of the Liver recommend treatment of HBeAg-negative patients until HBsAg loss, with or without HBsAb seroconversion.[6] However, the guidelines also suggest considering therapy cessation in noncirrhotic patients treated for at least 3 years with undetectable HBV DNA for at least 18 months. Treatment is indefinite if cirrhosis is present. Guidelines from the Asian Pacific Association for the Study of the Liver (APASL) recommend treatment until HBsAg loss following either anti-HBsAb seroconversion or at least 12 months of consolidation.[7] The guidelines indicate that one may consider stopping therapy if the patient has been on treatment for at least 2 years with undetectable HBV DNA documented on 3 occasions, each 6 months apart. They add that this may be considered in patients with compensated cirrhosis with close monitoring.

A multicenter study in Canada compared clinical characteristics of patients with CHB who were stratified into HBsAg loss (HBsAg-negative) with quantitative HBsAg less than 100 IU/mL or quantitative HBsAg greater than 100 IU/mL.[8] A total of 6882 patients were selected from the Canadian HBV Network. Only 4% (283/6882) had spontaneous or treatment-induced HBsAg loss. The majority of these patients had quantitative HBsAg less than 100 IU/mL, indicating that this cutoff level is predictive.

In pursuing functional cure in HBeAg-negative patients by ceasing NA therapy, the possibility of HBV reactivation leading to liver failure has gained attention.[4] Reactivation of HBV, characterized by a rise in HBV DNA by at least 1 log compared with baseline, may be spontaneous or triggered by chemotherapy, immunosuppression, solid organ transplantation, or discontinuation of antiviral medication.[3] Instances of acute liver failure (ALF) owing to reactivation of HBV have been described in patients receiving anticancer therapy and cytotoxic therapy.[3] However, ALF from discontinuation of NA therapy is rare and usually occurs in patients with impaired hepatic reserve because of cirrhosis.[1]

Nuc-STOP Approach to Therapy

A recent, large, prospective trial investigating NA therapy withdrawal in CHB HBeAg-negative patients who met the APASL cessation criteria found that 42 of 691 patients (308 with cirrhosis) who stopped therapy experienced seroconversion of HBsAg during a median follow-up of 155 weeks.[2] The estimated annual incidence of seroconversion was 1.78% in patients who stopped therapy compared with 0.15% in patients who did not. Seven of the 308 patients with cirrhosis who stopped therapy developed hepatic decompensation, and 3 died. In 9 other NA therapy withdrawal trials, 11 (0.2%-1.6%) patients experienced liver-related deaths.[4]

Nuc-STOP (The Norwegian Nucleoside Analogue Stop Study) enrolled 127 CHB HBeAg-negative patients with no history of cirrhosis who were suppressed on antiviral treatment for at least 24 months and who stopped antiviral therapy.[9] The median duration of antiviral treatment before inclusion was 45 months (interquartile

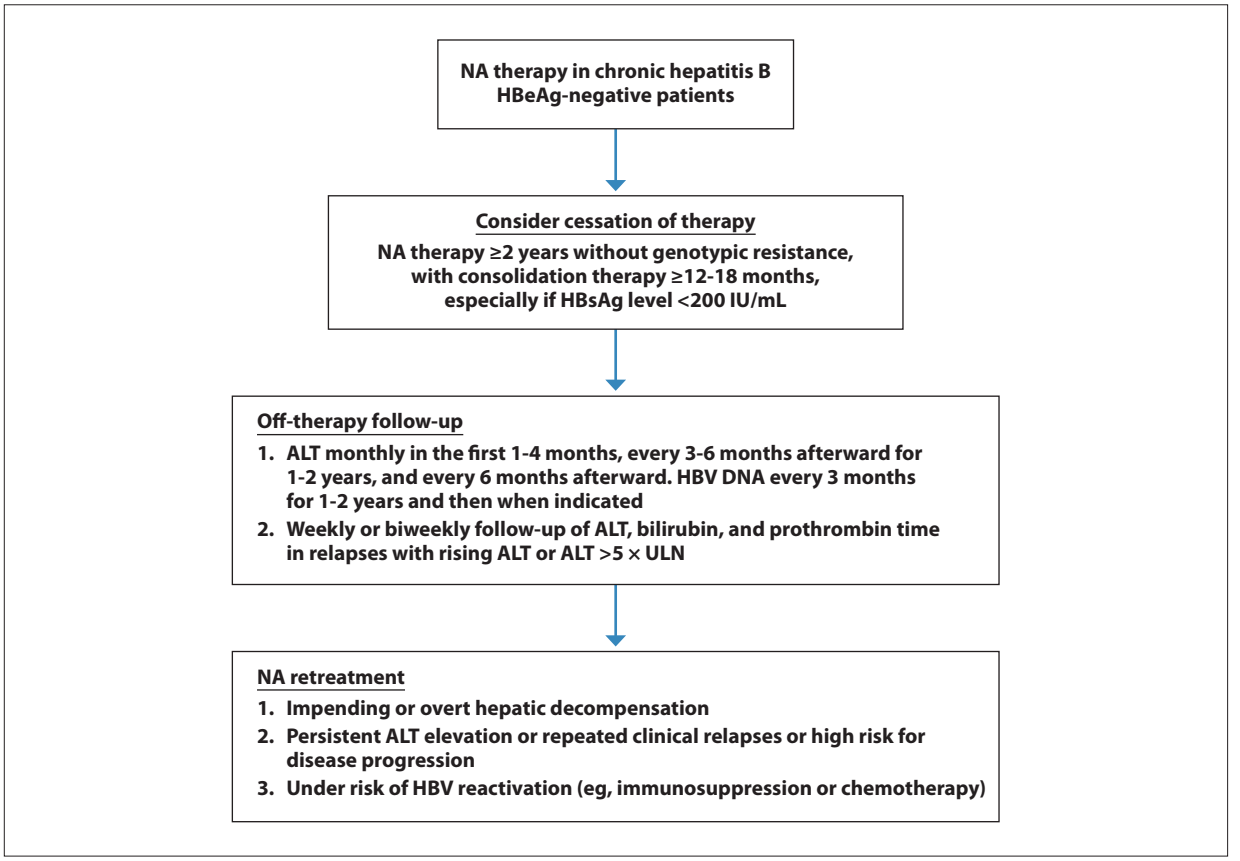

Figure 2. The recommended strategy from the Asian Pacific Association for the Study of the Liver guidelines for cessation, follow-up, and recommencement of NA therapy in chronic hepatitis B HBeAg-negative patients. Clinical relapse is defined as HBV DNA level ≥2000 IU/mL and serum ALT level >2 × ULN. Adapted from Chang et al.[14]

ALT, alanine aminotransferase; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, nucleoside/nucleotide analogue; ULN, upper limit of normal.

range, 32-76), and 90 (70.9%) patients were treated with tenofovir and 30 (23.6%) patients with entecavir. The primary endpoint of the study has not been reported; however, safety results were presented at the 2021 European Association for the Study of the Liver International Liver Congress. A total of 9 (7.1%) patients had a severe flare in the first year (1 patient with bilirubin >38 mmol/L) and all 9 cases of severe flare occurred among patients who stopped tenofovir therapy. The flares were not associated with age, sex, or duration of previous antiviral treatment. Eighty-five percent of the study cohort had a virologic relapse and 35% had a clinical relapse. Additional serious adverse events related to treatment interruption were not observed. Undetectable HBV DNA and normalized ALT levels were observed for 8 patients with severe flare after restart of therapy, and in 1 patient with spontaneous decline of HBV DNA without restarting therapy.

Data presented at the 2021 AASLD meeting on the HBV-STOP study evaluated clinical outcomes after stopping NA therapy in 110 noncirrhotic patients with CHB HBeAg-negative infection.[10] All patients had been on NA therapy for at least 18 months with an average treatment duration of greater than 2 years. Patients were monitored monthly for the first 3 months, then every 6 weeks for months 3 through 6, and then every 3 months for the remainder of the 96-week duration. All patients experienced HBV DNA reactivation after stopping NA therapy. Viral and biochemical rebound occurred earlier after tenofovir cessation compared with entecavir. HBsAg loss was observed in 7 of 110 patients and was associated with HBsAg levels less than 10 IU/L prior to stopping NA therapy.

A second multicenter study presented at the 2021 AASLD meeting quantified the incidence of severe acute exacerbations after cessation of NAs.[11] HBeAg-negative patients were included if they were older than 20 years of age, had a CHB infection for longer than 6 months, and were on NA therapy for at least 1 year prior to cessation. Severe acute exacerbations were defined as ALT greater than 5 times the upper limit of normal with bilirubinemia

greater than 2 mg/dL. A total of 830 eligible patients were observed for 34.7 months (interquartile range, 18.4-35.9). Thirty-eight patients developed a severe acute exacerbation, resulting in an annual rate of 1.14% (95% CI, 0.81%-1.57%) and cumulative severe acute exacerbation incidence of 6.6% (95% CI, 4.7%-9.2%) at 10 years. The study found that the risk of severe acute exacerbation was significantly higher within the first 2 years off treatment (P=.002). Factors associated with a significantly higher severe acute exacerbation risk included male sex and liver cirrhosis (P<.0001).

A third study presented at the 2021 AASLD meeting utilized deep sequencing and genome-length haplotype reconstruction to interrogate HBV sequences at baseline and following NA treatment cessation after a mean of 8 years of treatment.[12] Basal core promoter mutations at the *A1762T* and *G1764A* alleles were associated with an absence of an ALT flare following treatment cessation. Thus, sequencing for patients less likely to undergo a flare following treatment withdrawal may be a useful strategy.

The lack of reliable predictors of poor outcomes following NA therapy withdrawal complicates the pursuit of functional cure and is a critical area of future research.[4] However, large virologic studies of patients who develop ALF after NA withdrawal are unlikely to be performed in the United States, as such studies would create a significant risk for trial participants. Our group recently reported a case that suggested that both viral and host factors played roles in a patient with CHB HBeAg-positive infection, without cirrhosis, developing ALF after stopping tenofovir alafenamide without a physician's recommendation.[13] In that case, investigation of the viral genetics and host immune responses revealed that viral mutations known to promote virus replication were associated with reactivation, whereas adaptive immunity to HBV remained defective. This suggested that viral sequencing may be useful for identifying mutations that are unfavorable for therapy withdrawal. This case highlights the importance of off-therapy monitoring for patients who choose to stop NA treatment and suggests that continued therapy may be preferable for patients who are unable to adhere to a monitoring schedule.

Monitoring Patients Who Choose to Stop Nucleoside/Nucleotide Analogue Treatment

The only guidelines with off-treatment monitoring recommendations for providers are from APASL.[7] In a meta-analysis of 22 studies with a total of 1732 HBeAg-negative patients with CHB, the median duration of therapy, consolidation therapy, and off-therapy follow-up ranged from 6 months to 8 years, 4 to 96 weeks, and 6 to 80 months, respectively.[14] Patients were monitored for serum ALT and HBV DNA levels monthly during the first 1 to 3 months and every 3 to 6 months thereafter in most studies. One-year off-therapy virologic relapse (HBV DNA >2000 IU/mL) and clinical relapse (HBV DNA >2000 IU/mL and ALT elevation) occurred in less than 70% and less than 50% of patients, respectively, and less than 40% of the patients received retreatment. These rates were higher in patients with shorter treatment and shorter consolidation therapy (<2 years) and in patients treated with less potent NAs. Off-therapy severe flares were rare, and hepatic decompensation was reported in only 1 patient with cirrhosis.

The APASL guidelines state that biochemical relapse, which signifies enhanced killing of immune-mediated hepatocytes, may result in off-therapy HBsAg seroclearance, which is desirable.[14] Thus, with an appropriate stopping rule and a proper off-therapy monitoring plan, cessation of long-term NA therapy prior to HBsAg seroclearance in CHB HBeAg-negative infection is a feasible alternative to indefinite treatment. This strategy is summarized in Figure 2. More recently, the APASL published an updated guidance on NA cessation in patients with CHB, recommending HBV DNA and ALT measurements at least every 1 to 3 months until 12 months postcessation.[15] Because the median time to relapse is approximately 7 months after the end of treatment, we suggest that testing should be monthly in the first 4 months, every 3 months for months 5 through 12, and every 3 to 6 months thereafter. More stringent testing after treatment cessation may better secure patient safety.

Conclusion

Lifelong treatment with NAs has been the standard of care for most patients with CHB infection. Recently, however, withdrawal of NAs has started to be considered with the goal of achieving a functional cure. This approach has been tested in small trials and, although successful in some patients, has been shown to have unpredictable risks, including severe hepatitis flares, hepatic decompensation, and death. Further studies are required to understand the viral and host immune responses of patients with ALF participating in CHB therapy withdrawal in order to help predict the risk of flare. After reviewing the current literature, we believe that until further studies are performed, providers should tell patients that cessation of NA therapy is not without risks. Detailed discussion about the pros and cons of this strategy is required before coming to a joint decision with patients.[16-20]

Disclosures

Dr Pockros has served on the advisory boards for Gilead, AbbVie, Intercept, and Antios Therapeutics; as a data safety

monitoring board chair or member for Boston Pharmaceuticals, 89bio, and Altimmune; and as a speaker for Intercept. Dr Mulgaonkar has no relevant conflicts of interest to disclose.

References

1. Van Hees S, Bourgeois S, Van Vlierberghe H, et al; Belgian NA Stop Study Group. Stopping nucleos(t)ide analogue treatment in Caucasian hepatitis B patients after HBeAg seroconversion is associated with high relapse rates and fatal outcomes. *Aliment Pharmacol Ther*. 2018;47(8):1170-1180.
2. Jeng WJ, Chen YC, Chien RN, Sheen IS, Liaw YF. Incidence and predictors of hepatitis B surface antigen seroclearance after cessation of nucleos(t)ide analogue therapy in hepatitis B e antigen-negative chronic hepatitis B. *Hepatology*. 2018;68(2):425-434.
3. 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(4):1560-1599.
4. Liem KS, Gehring AJ, Feld JJ, Janssen HLA. Challenges with stopping long-term nucleos(t)ide analogue therapy in patients with chronic hepatitis B. *Gastroenterology*. 2020;158(5):1185-1190.
5. Rinker F, Zimmer CL, Höner Zu Siederdissen C, et al. Hepatitis B virus-specific T cell responses after stopping nucleos(t)ide analogue therapy in HBeAg-negative chronic hepatitis B. *J Hepatol*. 2018;69(3):584-593.
6. 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(2):370-398.
7. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int*. 2016;10(1):1-98.
8. Coffin CS, Haylock-Jacobs S, Doucette K, et al. Association between quantitative hepatitis B surface antigen levels (qHBsAg) and clinical outcomes of ethnically diverse Canadian chronic hepatitis B (CHB) patients: REtrospective and prospectiVe rEAL world evidence study of CHB in Canada (REVEAL-CANADA) [abstract 730]. Presented at: The Liver Meeting; November 12-14, 2021.
9. Johannessen A, Reikvam DH, Aleman S, et al. One-year safety results of the Nuc-Stop Study, an open-label study on stopping antiviral therapy in HBeAg negative chronic hepatitis B. *J Hepatol*. 2021;75(2):S734.
10. Hall S, Burns G, Anagnoston D, et al. Final results of the HBV-STOP study: low baseline HBsAg levels predict disease remission & HBsAg loss after stopping nucleot(s)ide analogues in chronic hepatitis B e-antigen negative patients [abstract 787]. Presented at: The Liver Meeting; November 12-14, 2021.
11. Wu J-L, Tseng C-H, Nguyen MH, et al. Severe acute exacerbation after cessation of nucleos(t)ide analogues for chronic hepatitis B: a real-world study of routine practice [abstract 806]. Presented at: The Liver Meeting; November 12-14, 2021.
12. Littlejohn M, Yuen Y, Wagner J, et al. Identifying virological factors associated with hepatitis B virus rebound following withdrawal of tenofovir therapy [abstract 871]. Presented at: The Liver Meeting; November 12-14, 2021.
13. Zhang H, Chen F, Giang E, et al. Virus reactivation in a non-cirrhotic HBV patient requiring liver transplantation after cessation of nucleoside analogue therapy. *Antivir Ther*. 2021;26(1-2):3-8.
14. Chang ML, Liaw YF, Hadziyannis SJ. Systematic review: cessation of long-term nucleos(t)ide analogue therapy in patients with hepatitis B e antigen-negative chronic hepatitis B. *Aliment Pharmacol Ther*. 2015;42(3):243-257.
15. Kao JH, Jeng WJ, Ning Q, et al. APASL guidance on stopping nucleos(t)ide analogues in chronic hepatitis B patients. *Hepatol Int*. 2021;15(4):833-851.
16. Yuen M-F, Berliba E, Sukeepaisarnjaroen W, et al. Repeat dosing of the GalNAc-siRNA AB-729 in subjects with chronic hepatitis B results in robust and sustained HBsAg suppression. *J Hepatol*. 2021;75(2):S203.
17. Gane E, Lim Y-S, Cloutier D, et al. Safety and antiviral activity of VIR-2218, an X-targeting RNAi therapeutic, in participants with chronic hepatitis B infection: week 48 follow-up results. *J Hepatol*. 2021;75(2):S287.
18. Gane E, Locarnini S, Lim TH, et al. Short interfering RNA JNJ-3989 combination therapy in chronic hepatitis B shows potent reduction of all viral markers but no correlate was identified for HBsAg reduction and baseline factors. *J Hepatol*. 2021;75(2):S289-S290.
19. Mani N, Cole AG, Kultgen SG, et al. Preclinical antiviral profile of AB-836, a potent, highly selective hepatitis B virus capsid inhibitor. *J Hepatol*. 2021;75(2):S291.
20. Thi EP, Yuen M-F, Gane E, et al. Inhibition of hepatitis B surface antigen by RNA interference therapeutic AB-729 in chronic hepatitis B patients correlates with suppression of all HBsAg isoforms and HBV RNA. *J Hepatol*. 2021;75(2):S760-S761.