ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2021 August 26; 9(24): 6964-7291

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 9 Number 24 August 26, 2021

OPINION REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Case Control Study

Retrospective Cohort Study

Retrospective Study

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 24 August 26, 2021

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 24 August 26, 2021

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 24 August 26, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Vijaykumar Chava, MD, Professor, Department of Periodontology, Narayana Dental College and Hospital, Nellore 524003, Andhra Pradesh, India. chava7@hotmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJCC* as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ji-Hong Liu*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
August 26, 2021

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2021 August 26; 9(24): 6979-6986

DOI: 10.12998/wjcc.v9.i24.6979

ISSN 2307-8960 (online)

MINIREVIEWS

Discontinuation of antiviral therapy in chronic hepatitis B patients

Renato Medas, Rodrigo Liberal, Guilherme Macedo

ORCID number: Renato Medas 0000-0002-1892-2666; Rodrigo Liberal 0000-0003-2525-1546; Guilherme Macedo 0000-0002-9387-9872.

Author contributions: Medas R and Liberal R developed the concept, planned the manuscript, performed the literature review, and created the first draft; Macedo G performed critical expert review and revision of the manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin:

Renato Medas, Rodrigo Liberal, Guilherme Macedo, Department of Gastroenterology and Hepatology, Centro Hospitalar Universitário de São João, Porto 4200-319, Portugal

Corresponding author: Rodrigo Liberal, MD, PhD, Assistant Professor, Senior Lecturer, Department of Gastroenterology and Hepatology, Centro Hospitalar Universitário de São João, Alameda Prof. Hernâni Monteiro, Porto 4200-016, Portugal. roliberal@hotmail.com

Abstract

Nucleos(t)ide analogs (NUC) are the first-line therapy for patients with chronic hepatitis B (CHB) recommended by most current guidelines. NUC therapy decreases progression of liver disease, reduces the risk of liver-related complications, and improves the quality of life of patients with CHB. Although indefinite or long-term NUC therapy is usually recommended, this strategy raises several concerns, such as side-effects, adherence, costs, and patient willingness to stop therapy. Recent data showed the feasibility, efficacy, and safety of stopping antiviral therapy in carefully selected CHB patients, leading to its incorporation in international guidelines. Patients who discontinue NUC have a higher likelihood of hepatitis B surface antigen (HBsAg) loss compared to patients who continue on therapy. Recommendations pertaining endpoints allowing safety discontinuation of NUC therapy differ among international guidelines. For hepatitis B e antigen (HBeAg)-positive patients, durable HBeAg seroconversion is considered an acceptable treatment endpoint. For HBeAg-negative patients, some guidelines propose undetectability hepatitis B virus DNA for at least 2 or 3 years, while others consider HBsAg loss as the only acceptable endpoint. CHB patients who stop therapy should remain under strict clinical and laboratorial follow-up protocols to detect and manage relapses in a timely manner. No reliable predictor of relapse has been consistently identified to date, although quantitative HBsAg has been increasingly studied as a reliable biomarker to predict safe NUC discontinuation.

Key Words: Chronic hepatitis B; Finite therapy; Hepatitis B surface antigen loss; Relapse; Retreatment

Core Tip: Recent data support the idea of stopping antiviral therapy in chronic hepatitis B patients. Current guidelines suggest that discontinuation of antiviral therapy may be

Portugal

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 29, 2021
Peer-review started: January 29, 2021
First decision: May 13, 2021
Revised: May 29, 2021
Accepted: July 2, 2021
Article in press: July 2, 2021
Published online: August 26, 2021

P-Reviewer: El-Shabrawi MH, Gupta T, Tanwandee T
S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Xing YX

attempted in non-cirrhotic patients who achieved durable on-therapy virological remission. Available evidence has shown that the paradigm shift from indefinite to finite antiviral therapy in chronic hepatitis B patients is emerging.

Citation: Medas R, Liberal R, Macedo G. Discontinuation of antiviral therapy in chronic hepatitis B patients. *World J Clin Cases* 2021; 9(24): 6979-6986
URL: https://www.wjgnet.com/2307-8960/full/v9/i24/6979.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i24.6979

INTRODUCTION

Chronic hepatitis B virus (HBV) infection is a major public health issue leading to chronic liver-disease, progression to cirrhosis and related complications[1]. Since 1990, several treatments have been approved for HBV treatment, which lead to lesser risk of developing cirrhosis, end-stage liver disease, hepatocellular carcinoma, and death[1].

Both nucleos(t)ide analogs (NUC) and pegylated interferon are recommended therapies for patients with chronic hepatitis B (CHB); however, NUCs are generally preferred therapy, particularly in Europe, due to easier administration, efficacy, and safety profile[2]. CHB therapy aims to reduce viral replication, decreasing progression of liver disease and the risk of liver-related complications. It also improves quality of life[3]. The ideal endpoint of NUC therapy is hepatitis B surface antigen (HBsAg) loss, with or without seroconversion to anti-HBs, however infrequently achievable with the current antiviral agents. Although they can suppress HBV DNA profoundly, they have no or little direct action on covalently closed circular DNA, which persist in the nucleus of infected hepatocytes as stable template for HBV production[4].

For this reason, long-term or indefinite NUC therapy is required in most patients. It has been shown that patients with CHB receiving long-term NUC therapy have excellent overall and liver-related survival, similar to general population[5]. However, such strategy raises some concerns, such long-term side-effects, adherence, costs, and patient willingness to stop therapy.

Over the last decade, emerging data were published to guide stopping antiviral therapy in selected CHB patients, which leads to its inclusion in international practicing guidelines of HBV management[6-8].

This review aims to resume the recommendations of current international guidelines on NUC discontinuation, including patient selection, safety, efficacy, surveillance, and indications for retreatment.

NUC THERAPY DISCONTINUATION: CURRENT RECOMMENDATIONS

Currently, the three most important international scientific societies [European Association for the Study of the Liver (EASL), American Association for the Study of the Liver Diseases (AASLD), and Asian Pacific Association for the Study of Liver (APASL)] have different criteria to stop NUC therapy in CHB[6-8].

As mentioned earlier, the ideal endpoint of NUC therapy is sustained HBsAg loss, with or even without seroconversion to anti-HBs[9]. Regarding this endpoint, all societies agree on the recommendation that all patients with CHB, including those with compensated cirrhosis, can discontinue NUC therapy if they achieve HBsAg loss that persists for at least 1 year[6-8]. Unfortunately, this endpoint is rarely achieved[9].

To overcome this problem, alternative endpoints have been developed, aiming to identify patients with satisfactory responses to NUCs who could benefit from stopping therapy without compromising the optimal management of CHB. However, there is no consensual approach among the international societies[6-8].

In non-cirrhotic hepatitis B e antigen (HBeAg)-positive patients, durable HBeAg seroconversion is considered a reliable indicator of sustained response after NUC discontinuation[10]. So, all current guidelines suggest stopping antiviral therapy if seroconversion of HBeAg to anti-HBe is achieved, along with HBV DNA undetectable and normal alanine aminotransferase (ALT) levels, after at least 12 mo of consolidation therapy (up to 3 years according to APASL)[6-8].

In non-cirrhotic HBeAg-negative patients, the EASL guidelines suggest stopping NUCs if the patient had undetectable HBV DNA for at least 3 years and if post-treatment follow-up is guaranteed for at least 1 year[7]. Although AASLD does not recommend NUC suspension in non-cirrhotic HBeAg-negative patients, they included a recommendation of NUC discontinuation if there is a compelling rationale and under careful monitoring every 3 mo for at least 1 year[8]. APASL suggests stopping therapy after at least 2 years of treatment if HBV DNA is undetectable on three separate samples, 6 mo apart[6].

In cirrhotic patients, both EASL and AASLD suggest indefinite long-term therapy while HBsAg persist positive[7,8]. On the other hand, APASL is the only organization to consider stopping NUC therapy in cirrhotic patients if the disease is compensated and under a careful monitoring plan[6]. Table 1 summarizes current recommendations on discontinuation of antiviral therapy in CHB patients by EASL, AALSD, and APASL.

SURVEILLANCE AFTER CESSATION OF NUCS

Several studies have shown an important number of patients having virological and clinical relapse after NUC discontinuation. Although some relapses can be beneficial to achieve HBsAg loss, others can induce hepatitis flare with progression to hepatic decompensation. To avoid undesirable outcomes, a close monitoring plan is mandatory, even though the optimal follow-up regimen is still not known.

Globally, HBeAg-positive CHB patients who achieved durable HBeAg seroconversion experience less relapses compared to HBeAg-negative CHB patients, allowing a less restricted surveillance[11,12]. After stopping NUC therapy, HBeAg-positive CHB patients should be monitored with ALT and HBV DNA determinations every 3 mo (monthly during the first 3 mo) and evaluation of HBeAg status every 3-6 mo[13-15].

Considering the higher probability of relapse of HBeAg-negative CHB patients, especially in the first 3 mo after antiviral therapy cessation, a more restrict protocol should be implemented. Thus, HBeAg-negative CHB patients should have ALT and HBV DNA determinations every 1-1.5 mo (during the first 3 mo), then every 3 mo until the end of first year. After that, surveillance every 6-12 mo can be considered[6].

Of note, APASL guidelines recommend that patients with hepatitis flare criteria [aspartate aminotransferase or ALT > 5 times greater "upper limit of normal" (ULN)] should be monitored weekly or biweekly with ALT, bilirubin, and prothrombin time to access the need for retreatment[6].

More recently, some studies associated a declining HBsAg quantification (qHBsAg) as a predictor to HBsAg loss and virological remission[16-18]. Based on these findings, some experts suggest determination of qHBsAg every 3-6 mo (more frequently in case of clinical relapse) to help retreatment decision based on off-treatment HBsAg/ALT kinetics[19].

After the first year off-treatment, the incidence of relapse is lower, allowing a surveillance similar to patients HBeAg-negative chronic HBV infection (inactive carrier in old terminology) with ALT and HBV DNA determinations every 3-6 mo or 6-12 mo in cases with HBV DNA ≥ 2000 or < 2000 IU/mL, respectively[7]. To access the functional cure (HBsAg loss), annual HBsAg assay can be considered.

As additional measures, periodic liver elastography and hepatocellular carcinoma surveillance should be maintained[7].

OFF-TREATMENT HBSAG LOSS

HBsAg seroclearance, with or without seroconversion to anti-HBs, is the ideal endpoint of NUC therapy, denominated functional cure. Even without therapy HBsAg loss can occur spontaneously, but the reported rates are variable, ranging from 0.12% to 2.38%[20,21].

Although NUC therapy can profoundly suppress HBV DNA, the reported rates of HBsAg loss are disappointing, persisting as a quite rare event. A recent meta-analysis (including 34 studies, 23 of them from Asia Pacific region) showed annual seroclearance rates varying from 0.15% to 3.02%, with a pooled rate of 1.02%[22].

Surprisingly, NUC therapy discontinuation (mostly in HBeAg-negative CHB patients) presented as a turning point in the probability of achieving HBsAg seroconversion. In a European study, the cumulative rate of HBsAg loss was around 25% at 18

Table 1 Recommendations on discontinuation of antiviral therapy in chronic hepatitis B patients by the European Association for the Study of Liver, American Association for the Study of Liver, and Asian Pacific Association for the Study of Liver guidelines

	HBeAg-positive	HBeAg-negative	Cirrhosis
EASL (2017)	HBsAg seroclearance	HBsAg seroclearance	No recommendation until HBsAg loss
	HBeAg seroconversion and HBV DNA undetectable with at least 12 mo of consolidation therapy	May be consider before HBsAg loss if undetectable HBV DNA for at least 3 yr (close monitoring for at least 1 yr)	
AASLD (2018)	HBsAg seroclearance	HBsAg seroclearance (close monitoring every 3 mo for at least 1 yr)	No recommendation until HBsAg loss
	HBeAg seroconversion with at least 12 mo of persistent ALT levels and undetectable HBV DNA (close monitoring every 3 mo for at least 1 yr)	May be consider if there is a compelling rationale and under careful monitoring every 3 mo for at least 1 yr	
APASL (2015)	HBeAg seroconversion with undetectable HBV DNA and persistently normal ALT levels with at least 1 yr of consolidation therapy (preferably 3 yr)	HBsAg seroclearance with anti-HBs seroconversion or at least 12 mo of a post-HBsAg clearance consolidation period	May be consider before HBsAg loss if disease is compensated and under a careful monitoring plan
		-After treatment for at least 2 yr with undetectable HBV DNA documented on 3 separate occasions, 6 mo apart	

AALSD: American Association for the Study of Liver; APASL: Asian Pacific Association for the Study of Liver; EASL: European Association for the Study of Liver; HBeAg: Hepatitis B e antigen.

mo off-therapy[23]. These results are in line with previous satisfactory results reported in other studies, in which cumulative rates of HBsAg loss of 39% at 5 years[24], 20% at 4 years[25], and 19% at 3 years[26] were reported.

Data from Asian patients have shown worse results, reporting a lower HBsAg rate loss compared to studies performed in the West. One study reported a cumulative rate of HBsAg loss of 16% at 6 years[18], and another study reported a rate of 13% at 5 years[27]. An earlier study was slightly more optimistic, reporting an overall probability of HBsAg seroclearance of 23% at 5 years[16]. A recent multicentric study of CHB patients (572 patients, 115 non-Asians), who included several ethnicities, showed higher virologic response rates (77/115, 67% *vs* 190/457, 42%; $P < 0.001$) and higher HBsAg loss rates (14.8% *vs* 1.5%; $P < 0.001$) in non-Asians compared to Asians, respectively[28].

These results may be due to not negligible differences between populations, like predominant genotype and age of acquisition of the infection[29].

Several additional factors seem to be determinant to achieve HBsAg seroclearance. A large study, including 691 patients, showed that end of treatment (EOT) qHBsAg level < 100 IU/mL, qHBsAg reduction from start to EOT > 1 Log10 IU/mL, and "no-retreatment" were three independent factors for HBsAg seroclearance after stopping NUCs[30]. This study consolidated preliminary results from previous studies who associated qHBsAg below 100 IU/mL to higher rates of HBsAg loss[16]. This trend was supported by other two studies that showed that the lesser qHBsAg level (especially < 100 IU/mL), the higher was the probability of achieving HBsAg seroclearance within the first 1 to 2 years of follow-up[17,31].

"No retreatment" upon a clinical relapse was described as a strong predictor of HBsAg loss[24]. Several studies showed substantial differences between the "retreat" *vs* "no-retreat" groups, after a relapse. One study showed a 6-year HBsAg loss rate of 19% in patients with clinical relapse who remained off-therapy, compared to only 1% in patients who were retreated (hazard ratio = 8.4; $P < 0.01$)[18]. The results in other study were similar, with "no-retreatment" patients having a 5-year HBsAg loss rate of 18% *vs* 0% in "retreatment" patients (hazard ratio = 18.6; $P < 0.001$)[27].

RELAPSE

Criteria for virological or clinical relapse was proposed by Asian-Pacific guidelines serving as guidance for several studies. Virological relapse (VR) is defined as serum HBV DNA above 2000 IU/mL, and clinical relapse (CR) is defined as VR relapse along with ALT above 2x ULN[6].

Remission assessment in patients who stop NUC therapy remains challenging since most studies differ widely in study populations, design, and duration of follow-up[11,32,33]. Criteria for relapse or/and retreatment also varies among studies.

A systematic review, including 1732 HBeAg-negative patients (22 studies), showed a VR rate < 70% and a CR < 50% in most studies. These rates tended to be lower in cases of longer treatment or consolidation therapy. CR happened most frequently within 6-mo off-therapy in patients treated with tenofovir, while for those treated with entecavir it occurred more frequently beyond 6-mo after stopping treatment[33]. Another systematic review showed a pooled rate of virologic remission at 1-year/2-year off-treatment of 63%/53% in HBeAg-positive CHB patients and 44%/31% in HBeAg-negative CHB patients[11].

Although not consistent between all studies, several factors were pointed as predictors of remission. In HBeAg-negative CHB patients, younger age, earlier disease stage, higher levels of ALT at baseline and at EOT, lower serum HBV DNA levels at baseline, low serum HBsAg levels at EOT, and decreasing HBsAg levels during treatment have been associated with a better chance of sustained remission[11].

Significant complications as severe flares and hepatic decompensation were infrequent (0.8% patients with cirrhosis); jaundice occurred in 2.5% and only 1 patient died from liver failure[11,33]. Considering all above, NUC therapy cessation seems to be feasible and safe, if adequate monitoring is implemented.

RETREATMENT

During surveillance, a critical point after NUC cessation is identifying patients who would benefit from antiviral therapy reintroduction. A lack of consensual criteria may be due to heterogeneous results from the published studies[11].

In brief, indications for retreatment can be grouped in two settings: Acute hepatitis flare or persistent mild to moderate hepatitis activity. The indications for retreatment in hepatitis flares are controversial since disease outcomes are variable[34]. On one hand, a too late retreatment decision may be detrimental, leading to development of liver decompensation and related complications. On the other hand, a too early retreatment decision may decrease the possibility of achieving HBsAg seroconversion, since it may prevent the "positive" relapse-associated induction of HBsAg loss[18]. Additionally, hepatitis flare may resolve spontaneously, and "no-retreatment decision" was identified as a strong predictor for off-treatment HBsAg loss[24,26,27,30].

Since hepatic decompensation is the most feared complication, it is mandatory to treat patients presenting with bilirubin > 2 mg/dL and/or INR > 1.5 to prevent unfavorable outcomes[6].

Albeit not standardized, some authors recommend also to retreat patients who present with ALT levels > 10 × ULN or ALT > 5 × ULN combined with increased bilirubin or prolongation of prothrombin time[10]. However, other authors recommend not using ALT levels alone as criteria to start retreatment, since some patients may have effective immune response against HBV that their hepatitis flare may subside along with decreasing HBV viremia and qHBsAg[35].

In real-world practice, patients with off-NUC hepatitis flare are mostly retreated with NUC upon presentation, which may hamper the probability of achieving functional cure. A study showed that patients with CR, which was not retreated, had a > 7 times higher incidence of HBsAg seroclearance than those who received retreatment[18].

Recent studies have focused on the role of HBsAg kinetics for retreatment decision guidance. It has been suggested that decreasing levels of qHBsAg during hepatitis flare, such as qHBsAg decline (> 10% than the preceding level) starting prior to or around the peak of ALT, may reflect host effective immune clearance of HBV is ongoing ("host-dominating flare"); if qHBsAg keeps increasing along with ascending ALT or if qHBsAg remains high after the peak of ALT, it may reflect that immune response is failing or being ineffective ("virus-dominating flare")[19,35,36]. Based on this immunological concept, HBsAg/ALT kinetics may be useful for determination of ideal subset of patients who may benefit retreatment during hepatitis flare[37].

Retreatment decision in persistent mild to moderate hepatitis activity is easier and has more consensus between clinicians. Usually, the criteria for retreatment are elevated ALT and HBV DNA > 2000 IU/mL for at least 3-6 mo[6-8]. One study suggests also retreating patients with modest ALT elevations (> 3 × ULN) and high HBV DNA levels (> 100000 IU/mL) at the same visit[23]. Either way, the highest

priority during patient monitoring should be safety, offering prompt retreatment timely based on actual data.

CONCLUSION

HBsAg loss remains the safest endpoint for discontinuing NUC therapy. Due to limited HBsAg loss rate on NUC therapy, other feasible endpoints are gaining interest in clinical practice. Evidence accumulating over the last decade supports the idea of stopping NUC therapy in patients with CHB who remain HBsAg positive. Most current guidelines already suggest that discontinuation of NUC therapy may be attempted in non-cirrhotic patients who achieved durable on-therapy virological remission, *i.e.* at least 3 years of non-detectable HBV DNA in HBeAg-negative patients or HBeAg seroconversion for HBeAg-positive patients. HBsAg loss seems to occur in an increasing proportion of patients off-NUC therapy, particularly in non-Asian patients. Patients in whom NUC therapy is discontinued should however remain under strict clinical and laboratorial follow-up protocols to detect and manage relapses in a timely manner. In addition, patients should be highly motivated for more frequent surveillance and should not have advanced fibrosis. Predefined criteria for retreatment are important. Recent evidence suggests that, in addition to surveillance strategies recommend by international guidelines, qHBsAg and ALT kinetics during hepatitis flares are useful for retreatment decision. New and validation of current biomarkers that are associated with clinical outcomes are needed for the development of clinical algorithms so we move towards a treatment personalized approach in patients with CHB.

REFERENCES

1 **Seto WK**, Lo YR, Pawlotsky JM, Yuen MF. Chronic hepatitis B virus infection. *Lancet* 2018; **392**: 2313-2324 [PMID: 30496122 DOI: 10.1016/S0140-6736(18)31865-8]

2 **Cornberg M**, Lok AS, Terrault NA, Zoulim F; 2019 EASL-AASLD HBV Treatment Endpoints Conference Faculty. Guidance for design and endpoints of clinical trials in chronic hepatitis B - Report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference. *Hepatology* 2019 [PMID: 31713892 DOI: 10.1002/hep.31030]

3 **Marcellin P**, Wong DK, Sievert W, Buggisch P, Petersen J, Flisiak R, Manns M, Kaita K, Krastev Z, Lee SS, Cathcart AL, Crans G, Op den Brouw M, Jump B, Gaggar A, Flaherty J, Buti M. Ten-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B virus infection. *Liver Int* 2019; **39**: 1868-1875 [PMID: 31136052 DOI: 10.1111/Liv.14155]

4 **Levrero M**, Pollicino T, Petersen J, Belloni L, Raimondo G, Dandri M. Control of cccDNA function in hepatitis B virus infection. *J Hepatol* 2009; **51**: 581-592 [PMID: 19616338 DOI: 10.1016/j.jhep.2009.05.022]

5 **Papatheodoridis GV**, Sypsa V, Dalekos G, Yurdaydin C, van Boemmel F, Buti M, Goulis J, Calleja JL, Chi H, Manolakopoulos S, Loglio A, Siakavellas S, Gatselis N, Keskın O, Lehretz M, Savvidou S, de la Revilla J, Hansen BE, Kourikou A, Vlachogiannakos I, Galanis K, Idilman R, Colombo M, Esteban R, Janssen HLA, Berg T, Lampertico P. Eight-year survival in chronic hepatitis B patients under long-term entecavir or tenofovir therapy is similar to the general population. *J Hepatol* 2018; **68**: 1129-1136 [PMID: 29427727 DOI: 10.1016/j.jhep.2018.01.031]

6 **Sarin SK**, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmeci AK, Gane E, Hou JL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lim SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao JH. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; **10**: 1-98 [PMID: 26563120 DOI: 10.1007/s12072-015-9675-4]

7 **European Association for the Study of the Liver**. 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 [PMID: 28427875 DOI: 10.1016/j.jhep.2017.03.021]

8 **Terrault NA**, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; **67**: 1560-1599 [PMID: 29405329 DOI: 10.1002/hep.29800]

9 **Kim GA**, Lim YS, An J, Lee D, Shim JH, Kim KM, Lee HC, Chung YH, Lee YS, Suh DJ. HBsAg seroclearance after nucleoside analogue therapy in patients with chronic hepatitis B: clinical outcomes and durability. *Gut* 2014; **63**: 1325-1332 [PMID: 24162593 DOI: 10.1136/gutjnl-2013-305517]

10 **Papatheodoridi M**, Papatheodoridis G. Can we stop nucleoside analogues before HBsAg loss? *J Viral Hepat* 2019; **26**: 936-941 [PMID: 30803099 DOI: 10.1111/jvh.13091]

11 **Papatheodoridis G**, Vlachogiannakos I, Cholongitas E, Wursthorn K, Thomadakis C, Touloumi G,

Petersen J. Discontinuation of oral antivirals in chronic hepatitis B: A systematic review. *Hepatology* 2016; **63**: 1481-1492 [PMID: 27100145 DOI: 10.1002/hep.28438]

12 **Liem KS**, Fung S, Wong DK, Yim C, Noureldin S, Chen J, Feld JJ, Hansen BE, Janssen HLA. Limited sustained response after stopping nucleos(t)ide analogues in patients with chronic hepatitis B: results from a randomised controlled trial (Toronto STOP study). *Gut* 2019; **68**: 2206-2213 [PMID: 31462554 DOI: 10.1136/gutjnl-2019-318981]

13 **Yeh CT**, Hsu CW, Chen YC, Liaw YF. Withdrawal of lamivudine in HBeAg-positive chronic hepatitis B patients after achieving effective maintained virological suppression. *J Clin Virol* 2009; **45**: 114-118 [PMID: 19451024 DOI: 10.1016/j.jcv.2009.04.006]

14 **He D**, Guo S, Zhu P, Tao S, Li M, Huang H, Wang J, Wang Y, Ding M. Long-term outcomes after nucleos(t)ide analogue discontinuation in HBeAg-positive chronic hepatitis B patients. *Clin Microbiol Infect* 2014; **20**: O687-O693 [PMID: 25469947 DOI: 10.1111/1469-0691.12605]

15 **Song MJ**, Song DS, Kim HY, Yoo SH, Bae SH, Choi JY, Yoon SK, Paik YH, Lee JS, Lee HW, Kim HJ. Durability of viral response after off-treatment in HBeAg positive chronic hepatitis B. *World J Gastroenterol* 2012; **18**: 6277-6283 [PMID: 23180949 DOI: 10.3748/wjg.v18.i43.6277]

16 **Chan HL**, Wong GL, Chim AM, Chan HY, Chu SH, Wong VW. Prediction of off-treatment response to lamivudine by serum hepatitis B surface antigen quantification in hepatitis B e antigen-negative patients. *Antivir Ther* 2011; **16**: 1249-1257 [PMID: 22155906 DOI: 10.3851/IMP1921]

17 **Papatheodoridi M**, Hadziyannis E, Berby F, Zachou K, Testoni B, Rigopoulou E, Gatselis NK, Lyberopoulou A, Vlachogiannakos I, Manolakopoulos S, Dalekos GN, Zoulim F, Papatheodoridis GV. Predictors of hepatitis B surface antigen loss, relapse and retreatment after discontinuation of effective oral antiviral therapy in noncirrhotic HBeAg-negative chronic hepatitis B. *J Viral Hepat* 2020; **27**: 118-126 [PMID: 31562748 DOI: 10.1111/jvh.13211]

18 **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**: 425-434 [PMID: 29108132 DOI: 10.1002/hep.29640]

19 **Liaw YF**. Clinical utility of HBV surface antigen quantification in HBV e antigen-negative chronic HBV infection. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 631-641 [PMID: 31477873 DOI: 10.1038/s41575-019-0197-8]

20 **Liu J**, Yang HI, Lee MH, Lu SN, Jen CL, Wang LY, You SL, Iloeje UH, Chen CJ; REVEAL-HBV Study Group. Incidence and determinants of spontaneous hepatitis B surface antigen seroclearance: a community-based follow-up study. *Gastroenterology* 2010; **139**: 474-482 [PMID: 20434450 DOI: 10.1053/j.gastro.2010.04.048]

21 **Chu CM**, Liaw YF. HBsAg seroclearance in asymptomatic carriers of high endemic areas: appreciably high rates during a long-term follow-up. *Hepatology* 2007; **45**: 1187-1192 [PMID: 17465003 DOI: 10.1002/hep.21612]

22 **Yeo YH**, Ho HJ, Yang HI, Tseng TC, Hosaka T, Trinh HN, Kwak MS, Park YM, Fung JYY, Buti M, Rodríguez M, Treeprasertsuk S, Preda CM, Ungtrakul T, Charatcharoenwitthaya P, Li X, Li J, Zhang J, Le MH, Wei B, Zou B, Le A, Jeong D, Chien N, Kam L, Lee CC, Riveiro-Barciela M, Istratescu D, Sriprayoon T, Chong Y, Tanwandee T, Kobayashi M, Suzuki F, Yuen MF, Lee HS, Kao JH, Lok AS, Wu CY, Nguyen MH. Factors Associated With Rates of HBsAg Seroclearance in Adults With Chronic HBV Infection: A Systematic Review and Meta-analysis. *Gastroenterology* 2019; **156**: 635-646.e9 [PMID: 30342034 DOI: 10.1053/j.gastro.2018.10.027]

23 **Papatheodoridis GV**, Rigopoulou EI, Papatheodoridi M, Zachou K, Xourafas V, Gatselis N, Hadziyannis E, Vlachogiannakos J, Manolakopoulos S, Dalekos GN. DARING-B: discontinuation of effective entecavir or tenofovir disoproxil fumarate long-term therapy before HBsAg loss in non-cirrhotic HBeAg-negative chronic hepatitis B. *Antivir Ther* 2018; **23**: 677-685 [PMID: 30044765 DOI: 10.3851/IMP3256]

24 **Hadziyannis SJ**, Sevastianos V, Rapti I, Vassilopoulos D, Hadziyannis E. Sustained responses and loss of HBsAg in HBeAg-negative patients with chronic hepatitis B who stop long-term treatment with adefovir. *Gastroenterology* 2012; **143**: 629-636.e1 [PMID: 22659218 DOI: 10.1053/j.gastro.2012.05.039]

25 **Höner Zu Siederdissen C**, Rinker F, Maasoumy B, Wiegand SB, Filmann N, Falk CS, Deterding K, Port K, Mix C, Manns MP, Herrmann E, Wedemeyer H, Kraft AR, Cornberg M. Viral and Host Responses After Stopping Long-term Nucleos(t)ide Analogue Therapy in HBeAg-Negative Chronic Hepatitis B. *J Infect Dis* 2016; **214**: 1492-1497 [PMID: 27609808 DOI: 10.1093/infdis/jiw412]

26 **Berg T**, Simon KG, Mauss S, Schott E, Heyne R, Klass DM, Eisenbach C, Welzel TM, Zachoval R, Felten G, Schulze-Zur-Wiesch J, Cornberg M, Op den Brouw ML, Jump B, Reiser H, Gallo L, Warger T, Petersen J; FINITE CHB study investigators [First investigation in stopping TDF treatment after long-term virological suppression in HBeAg-negative chronic hepatitis B]. Long-term response after stopping tenofovir disoproxil fumarate in non-cirrhotic HBeAg-negative patients - FINITE study. *J Hepatol* 2017; **67**: 918-924 [PMID: 28736139 DOI: 10.1016/j.jhep.2017.07.012]

27 **Chen CH**, Hung CH, Wang JH, Lu SN, Lai HC, Hu TH, Lin CH, Peng CY. The Incidence of Hepatitis B Surface Antigen Loss Between Hepatitis B E Antigen-Negative Noncirrhotic Patients Who Discontinued or Continued Entecavir Therapy. *J Infect Dis* 2019; **219**: 1624-1633 [PMID: 30689910 DOI: 10.1093/infdis/jiy697]

28 **Sonneveld MJ**, Park JY, Kaewdech A, Seto WK, Tanaka Y, Carey I, Papatheodoridi M, van Bömmel F, Berg T, Zoulim F, Ahn SH, Dalekos GN, Erler NS, Höner Zu Siederdissen C, Wedemeyer H,

Cornberg M, Yuen MF, Agarwal K, Boonstra A, Buti M, Piratvisuth T, Papatheodoridis G, Maasoumy B; CREATE Study Group. Prediction of Sustained Response After Nucleo(s)tide Analogue Cessation Using HBsAg and HBcrAg Levels: A Multicenter Study (CREATE). *Clin Gastroenterol Hepatol* 2020 [PMID: 33309804 DOI: 10.1016/j.cgh.2020.12.005]

29 **Liaw YF**. Finite nucleos(t)ide analog therapy in HBeAg-negative chronic hepatitis B: an emerging paradigm shift. *Hepatol Int* 2019; **13**: 665-673 [PMID: 31559604 DOI: 10.1007/s12072-019-09989-6]

30 **Chi H**, Hansen BE, Yim C, Arends P, Abu-Amara M, van der Eijk AA, Feld JJ, de Knegt RJ, Wong DK, Janssen HL. Reduced risk of relapse after long-term nucleos(t)ide analogue consolidation therapy for chronic hepatitis B. *Aliment Pharmacol Ther* 2015; **41**: 867-876 [PMID: 25752878 DOI: 10.1111/apt.13150]

31 **Chen CH**, Hung CH, Wang JH, Lu SN, Hu TH, Lee CM. Long-term incidence and predictors of hepatitis B surface antigen loss after discontinuing nucleoside analogues in noncirrhotic chronic hepatitis B patients. *Clin Microbiol Infect* 2018; **24**: 997-1003 [PMID: 29288020 DOI: 10.1016/j.cmi.2017.12.013]

32 **Hadziyannis S**, Liaw YF. Discontinuation of long-term NA therapy in HBeAg-negative chronic hepatitis B. *Gut* 2015; **64**: 1005-1006 [PMID: 25410164 DOI: 10.1136/gutjnl-2014-308677]

33 **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**: 243-257 [PMID: 26151841 DOI: 10.1111/apt.13272]

34 **Chang ML**, Liaw YF. Hepatitis B flares in chronic hepatitis B: pathogenesis, natural course, and management. *J Hepatol* 2014; **61**: 1407-1417 [PMID: 25178562 DOI: 10.1016/j.jhep.2014.08.033]

35 **Liaw YF**. Hepatitis B Flare After Cessation of Nucleos(t)ide Analogue Therapy in HBeAg-Negative Chronic Hepatitis B: To Retreat or Not to Retreat. *Hepatology* 2021; **73**: 843-852 [PMID: 32810321 DOI: 10.1002/hep.31525]

36 **Chien RN**, Liaw YF. Re-treatment for severe hepatitis flare in HBeAg-negative chronic hepatitis B: An appraisal with combined HBsAg/ALT kinetics. *J Viral Hepat* 2020; **27**: 544-547 [PMID: 31868280 DOI: 10.1111/jvh.13253]

37 **Liaw YF**, Jeng WJ, Chang ML. HBsAg Kinetics in Retreatment Decision for Off-Therapy Hepatitis B Flare in HBeAg-Negative Patients. *Gastroenterology* 2018; **154**: 2280-2281 [PMID: 29746811 DOI: 10.1053/j.gastro.2018.03.066]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com