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## Challenges in the discontinuation of chronic hepatitis B antiviral agents

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### Abstract

Long-term antiviral treatment of chronic hepatitis B patients has been proven to be beneficial in reducing liver-related complications. However, lengthy periods of daily administration of medication have some inevitable drawbacks, including decreased medication adherence, increased cost of treatment, and possible long-term side effects. Currently, discontinuation of antiviral agent has become the strategy of interest to many hepatologists, as it might alleviate the aforementioned drawbacks and increase the probability of achieving functional cure. This review focuses on the current evidence of the outcomes following stopping antiviral treatment and the factors associated with subsequent hepatitis B virus relapse, hepatitis B surface antigen clearance, and unmet needs.

**Key Words:** Viral hepatitis B; Relapse; Retreatment; SCALE-B; Stop treatment strategy; Nucleoside analogs

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**Core Tip:** Stop strategy is one of the options to get closer to functional cure with a finite duration of treatment in chronic hepatitis B patients. Virological relapse and clinical relapse are common after stopping antiviral agent. Half the patients with clinical relapse require retreatment. Novel biomarkers and the SCALE-B score predict clinical relapse and hepatitis B surface antigen clearance. Knowing when to restart treatment and novel sensitive biomarkers are unmet needs.

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Hepatitis B virus (HBV) infection is a major health problem globally; approximately 292 million people are affected by this virus[1]. Patients with chronic hepatitis B (CHB) infection are at risk of developing long-term liver-related complications, *e.g.*, cirrhosis, decompensation, and malignant liver tumors[2]. Although the prevalence of CHB infection has declined as a result of immunization programs, the majority of Southeast Asian countries are still categorized as intermediately to highly endemic areas[3]. HBV replication occurs through the formation of covalently closed circular DNA (cccDNA), and the persistence of intrahepatic cccDNA is the major reason for disease chronicity and a major obstacle for the eradication of HBV[4]. However, the measurement of intrahepatic cccDNA is not practical in clinical practice as it can only be done through liver biopsy.

Long-term nucleos(t)ide analogs (NA) inhibit the reverse transcriptase activity of viral polymerase and effectively inhibit HBV replication, reverse liver fibrosis, and reduce the risk of hepatocellular carcinoma (HCC)[5,6]. However, NA have no direct effect on intrahepatic cccDNA or virus transcription in the liver. Therefore, because functional cure, defined as hepatitis B surface antigen (HBsAg) clearance with or without anti-HBs seroconversion, is not often achieved, and most patients need long-term or even lifelong NA therapy[7].

Currently, the best time to stop NA therapy before HBsAg clearance is still uncertain because of the high rates of nontreatment recurrence. For instance, the pooled analysis of a systematic review showed a virological relapse (VR) rate of about 50% to 60% within 12 to 36 mo after drug withdrawal[8]. Although recent clinical guidelines suggest that some patients may stop taking NA before achieving HBsAg serum clearance[9-11], sensitive and reliable biomarkers for identifying patients with low recurrence risk have not yet been established[12,13]. This review focuses on both benefits and risks of discontinuing antiviral agents, as well as the current recommendations, factors, and novel biomarkers for predicting outcomes following NA cessation, and unfulfilled demands.

**ADVANTAGES VS DISADVANTAGES OF ANTIVIRAL AGENT DISCONTINUATION**

Benefit and risk concerns of CHB antiviral cessation are summarized in **Figure 1**.

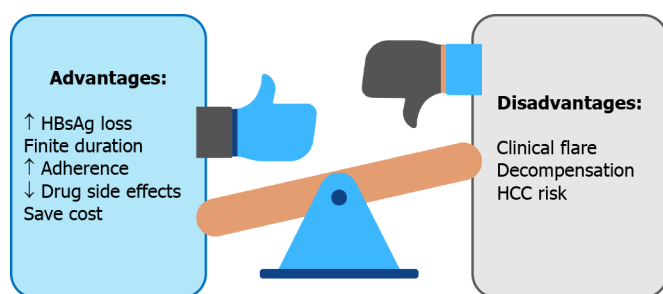
**Advantages**

**Increased HBsAg loss:** The ultimate goal of CHB treatment is clearance of intrahepatic cccDNA. Nonetheless, this endpoint seems to be unrealistic with the current treatment options[9-11]. A more pragmatic endpoint is HBsAg loss with undetectable HBV DNA or a so called "functional cure," yet HBsAg loss is rarely achieved with long-term NA therapy. In a French study of 18 CHB patients with NA treatment, the annual decrease of HBsAg levels was only 0.084 log<sub>10</sub> IU/mL[14], with a study-derived model predicting that HBsAg loss after continuous treatment with NA would be achieved in 52.2 years.

On the other hand, cessation of NA therapy may increase HBsAg clearance. An initial study by Hadziyannis *et al*[15] showed a high rate of HBsAg loss of 39.4% at 6 years after stopped adefovir (ADV) in hepatitis B e-antigen (HBeAg) negative CHB patients. That study was followed by a peak of interest in NA discontinuation[15]. A recent systematic review including 1085 patients reported a rate of HBsAg loss of approximately 8%[8]. In contrast, a subsequent study reported HBsAg loss in a minority of patients on continuous NA therapy, approximately 2.1% after 10 years of follow-up[16].

**Finite duration:** Generally, long-term treatment with NA is required, in contrast to the definable duration of interferon-based therapy, 12 mo in HBeAg-negative, and 6-12 mo in HBeAg-positive patients[17]. Even though the side effects after several years of medication are very few, they can be problematic in real-life practice. An attempt to define a limited duration of NA therapy was first proposed in the Asian Pacific Association for the Study of the Liver (APASL) 2008 guidelines[18]. Finite duration may increase drug adherence, lower the chances of developing side effects from the drug, and reduce costs[19].





**Figure 1 Advantages vs disadvantages of antiviral agent discontinuation in chronic hepatitis B.** HBsAg: Hepatitis B surface antigen; HCC: Hepatocellular carcinoma.

**Increased adherence:** Longer use of NA treatment is associated with lower medication compliance. Drug adherence is of concern in real-life practice[20]. Poor antiviral agent compliance is associated with emerging resistance, particularly in agents with a low genetic barrier[21]. A large retrospective study that included 11,100 CHB patients in the United States found a rate of adherence of 87%[20]. Moreover, a systematic review and meta-analysis included of 30 studies reported that the long-term adherence rate was only 74.7% after a median follow-up of 16 mo[22]. Notably, it was suboptimal compared with a good adherence rate of 95% defined in previous studies[20,23-25]. Compliance to antiviral agent use may improve with finite duration of treatment.

**Decreased side effects:** A recent systematic review indicated adverse events associated with NA were not common. However, some events were fatal, especially mitochondrial toxicity[26]. Long-term treatment with NA potentiates renal and bone side effects, particularly in tenofovir disoproxil fumarate (TDF) and ADV users. In addition to the well-known side effects of tubular dysfunction and Fanconi syndrome associated with TDF and ADV, the real-world data also found that the estimated glomerular filtration rate (eGFR) declined more quickly in TDF and ADV users than in untreated CHB patients[27]. Despite the observation in recent registration trials that tenofovir alafenamide (TAF) had significantly lower rates of bone mineral density and eGFR reduction compared with TDF[28,29], making it is safer for long-term use, the reported safety data were from follow-up of no longer than 96 wk[30]. Therefore, whether TAF is truly safe for extended treatment is yet to be confirmed. Nonetheless, as shorter time of exposure to NA would decrease the risk of side effects.

**Cost savings:** As mentioned above, hepatitis B treatment with NA might be a long-term therapy. According to a survey in Singapore, fewer than half the patients preferred lifelong treatment[31]. One of the most concerns of lifelong therapy is the cost of treatment. Moreover, only about a quarter of the patients were willing to pay for lifelong therapy, with an acceptable daily cost of 8 United States dollars.

### Disadvantages

**Clinical flare and decompensation following off-therapy:** The concerning issue after NA discontinuation is HBV flare, especially clinical relapse (CR). Most studies defined CR as an off-therapy HBV DNA > 2000 IU/mL plus an alanine aminotransferase (ALT) level > 2 times the upper limit of normal (ULN)[8,32]. The overall CR rate from a pooled data analysis with a follow-up ranging from 12-69 mo duration after NA discontinuation was 34.6% in which CR was higher in HBeAg-negative patients (43.7%) than in HBeAg-positive (23.8%)[8]. CR, particularly severe CR, may lead to jaundice, prolonged prothrombin time (PT), or eventually liver failure. In our study in Thai patients, two noncirrhotic HBeAg-negative patients developed jaundice (classified as severe CR) 3 mo after NA discontinuation[12]. Jaundice and hepatitis resolved in both patients after retreatment. Clinical decompensation and death following NA discontinuation has been reported in Asian studies; decompensation and fatality were observed in 0%-1.58% and 0%-0.19% in noncirrhotic patients at 1-3 years of follow-up, while there was a limited number of studies in cirrhotic patients [33-35]. The annual incidence of liver decompensation and death were recently reported to be 2.95% and 1%, respectively in cirrhotic patients who stopped NA[33]. Of interest, ENUMERATE study of the patients in the United States reported hepatic decompensation in five of 61 entecavir-treated patients (8.2%) after a median follow-up of 4 years[36]. Although not from a head-to-head comparison, the data are of

concern because liver decompensation in cirrhotic patients who stopped NA therapy seems to be numerically higher than in those who continued treatment. Thus, the current evidence indicates a need for vigilance after NA discontinuation in cirrhotic patients.

**HCC risk:** There are several well-known benefits of NA treatment in CHB patients[9-11]. Antiviral therapy with NA results in viral suppression, fibrosis improvement, and lower risk of HCC development[37]. Whether patients who stop NA will experience an increased occurrence of HCC in the future than those with continuous treatment is not clear. Nevertheless, to date, HCC development in patients who discontinued NA is not significantly higher than in those who continued NA treatment[33].

## GUIDELINE RECOMMENDATIONS

Currently, international practice guidelines for CHB management suggest that patients who had consecutive findings of undetectable HBV DNA for a certain duration can stop NA[9-11]. The expert consensus from the APASL first mentioned treatment discontinuation in 2008, advocating that NA therapy can be stopped in selected patients because of drug resistance concerns in long-term NA treatment[18]. The latest recommendations from international hepatology societies for considering stopping NA therapy are shown in Table 1.

In HBeAg-positive CHB patients, all guidelines allow NA discontinuation in patients who develop HBeAg seroconversion with persistent normal ALT levels and undetectable HBV DNA following consolidation therapy after e-seroconversion for at least 12 mo[38] or preferably 3 years in the APASL guidelines[11]. For patients who are HBeAg-negative, the APASL guideline states that NA can be withdrawn in noncirrhotic patients after treatment for at least 2 years, with an undetectable HBV DNA documented on three consecutive visits, 6 mo apart, or until HBsAg loss with or without development of anti-HBs[11]. Likewise, the European Association for the Study of the Liver (EASL) allows stopping NA in highly selected patients with 3 years of continuous suppression of HBV DNA in noncirrhotic patients[9]. On the contrary, the American Association for the Study of Liver Diseases (AASLD) recommend continuing NA treatment indefinitely unless HBsAg loss is achieved[10]. In patients with liver cirrhosis, the APASL recommends that the discontinuation of NA might be considered, but only with close monitoring[11].

## HBV RELAPSE AND PREDICTIVE FACTORS

HBV relapse is a common event after NA discontinuation and can be simply categorized into virological relapse (VR) and CR. Most of the studies defined HBV DNA greater than 2000 IU/mL as the definition of VR, and when in combination with an ALT of at least two times the ULN, CR is recognized. A systematic review by Papatheodoridis *et al*[8], reported VR rates of 51.4% and 38.2% at 1- and 3-year, respectively, after NA discontinuation. The occurrence of VR was higher in HBeAg-negative patients than in HBeAg-positive patients. The rates were 56.3% *vs* 37.5% and 69.9% *vs* 48.5% at 1- and 3-year, respectively. VR commonly occurred when NA was stopped, but VR alone might not have a clinically significant impact. In some patients, VR may be transient, with a spontaneous decline of viral replication resulting from an immune response. In contrast, a CR may require initiation of retreatment, or more importantly lead to severe flare, and hepatic failure. A randomized controlled study by Liem *et al*[39] reported that half the patients developed CR after NA discontinuation[39]. Consequently, three-quarters of the patients required retreatment. A summary of the studies reporting the occurrence of VR, CR, and HBsAg loss after NA discontinuation is shown in Table 2.

Various baseline and on-treatment factors are associated with VR off-therapy patients. At pretreatment, the baseline characteristics of increasing age and male sex have been associated with an increased relapse rate[40]. During treatment, extension of consolidation treatment duration by more than 1 to 3 years reduces the risk of VR in both HBeAg-positive and HBeAg-negative patients[38]. For that reason, the international guidelines recommend at least 1 year of consolidation therapy, and preferably 3 years in the APASL guidelines[11], after HBeAg seroconversion before considering NA discontinuation in HBeAg-positive patients. Moreover, the end of treatment (EOT) HBsAg level is highly predictive of HBV relapse, a higher level is correlated with a



**Table 1 Guidelines for stopping nucleos(t)ide analog therapy**

Guidelines	HBeAg-positive CHB	HBeAg-negative CHB
APASL 2015 [11]	HBeAg seroconversion: + undetectable HBV DNA + normal ALT for $\geq 12$ mo (or preferably 3 yr). Cirrhotic patients may be stopped with careful monitoring	Undetectable HBV DNA at least 2 yr with documented on three separate occasions, 6 mo apart: Or HBsAg clearance either at least for 1 yr; Or until anti-HBs seroconversion. Cirrhotic patients may be stopped with careful monitoring
AASLD 2018 [10]	HBeAg seroconversion + undetectable DNA + normal ALT for $\geq 12$ mo. Not recommended in cirrhosis	HBsAg clearance. Not recommended in cirrhosis
EASL 2017 [9]	HBeAg seroconversion + undetectable DNA for $\geq 12$ mo. Not recommended in cirrhosis	HBsAg clearance. Or selected noncirrhotic with undetectable HBV DNA $\geq 3$ yr. Not recommended in cirrhosis

AASLD: American Association for the Study of the Liver; ALT: Alanine aminotransferase; APASL: Asian Pacific Association for the Study of the Liver; CHB: Chronic hepatitis B; EASL: European Association for the Study of the Liver; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

higher HBV relapse rate[40,41].

From our point of view, the CR is more clinically important than VR, as it may be followed by liver-related complications. A study in a Thai cohort demonstrated that EOT hepatitis B core-related antigen (HBcrAg) and HBV RNA level were independent risk factors for the subsequent development of CR[12]. A recent meta-analysis including 1573 patients indicated that the higher pretreatment HBsAg levels were associated with shorter consolidation duration and the higher EOT HBsAg levels, especially those  $> 1000$  IU/mL, were independently associated with CR[33]. Many studies attempted to find factors associated with VR and CR, and the reported results are summarized in Table 3.

## HBsAg CLEARANCE AND PREDICTIVE FACTORS

HBsAg clearance is the desired goal of hepatitis B treatment. Nonetheless, as mentioned above, even if possible, it seldom occurs while on NA treatment, and stopping NA may be a strategy to increase the chance of HBsAg loss. A pivotal Greece study with 33 genotype D, HBeAg-negative patients who stopped ADV, HBsAg loss occurred in 13 of 33 patients (39.4%) after a 6-year follow-up[15]. In addition, the first small randomized controlled trial (RCT) from Germany reported HBsAg clearance in 4 of 21 HBeAg-negative CHB patients after 3-year of off-therapy[42]. However, another RCT conducted by Liem *et al*[39], in which the majority of the patients were Asian, HBsAg loss occurred in only one patient 1.5 years after NA cessation[39]. Ethnicity and HBV genotype may affect the rate of HBsAg loss.

A large retrospective Taiwanese study that included 691 patients, demonstrated a shorter time to undetectable HBV DNA (especially if assayed less than 12 wk after NA initiation), on-treatment reduction of HBsAg level of  $> 1 \log_{10}$  IU/mL, and an EOT HBsAg level of  $< 100$  IU/mL were independently associated with an increase in the likelihood of off-therapy HBsAg loss[33]. Furthermore, lower pretreatment ALT and HBV DNA levels, lower EOT HBsAg level, and longer treatment duration predicted HBsAg loss in another study[40]. The predictive factors for HBsAg loss in off-therapy patients are summarized in Table 4.

## NOVEL BIOMARKERS TO PREDICT HBV RELAPSE AND HBsAg CLEARANCE

### HBsAg quantification

Quantitative serum HBsAg (qHBsAg) has been around in the management of CHB for a while. In untreated patients, serum HBsAg quantification can help to define disease stage, predict spontaneous HBsAg clearance, and predict long-term liver-related complications[43]. As qHBsAg has been used in the clinical practice nowadays, commercial assay kits are widely available. There is increasing evidence of qHBsAg as a marker to aid physicians in deciding whether to discontinue NA. A Taiwanese study by Chen *et al*[40] found that a cutoff level of  $< 120$  IU/mL predicted HBsAg clearance in HBeAg-negative patients and  $< 300$  IU/mL in HBeAg-positive, respectively[40]. A systematic review by Liu *et al*[41] indicated that an EOT HBsAg level  $< 100$  IU/mL

**Table 2 Off-therapy virological relapse, clinical relapse, and hepatitis B surface antigen loss in chronic hepatitis B patients**

Ref.	Country	n (%)	HBeAg-negative, n (%)	Follow-up time (mo)	Virological relapse rate (%)	Clinical relapse rate (%)	HBsAg loss, n (%)
Fung <i>et al</i> [67], 2004	Canada	27	27	18	44.4	25.9	NR <sup>1</sup>
Enomoto <i>et al</i> [68], 2008	Japan	22	22	48	68.7	68.7	NR
Yeh <i>et al</i> [69], 2009	Taiwan	71	0	15	26.8	26.8	0
Fung <i>et al</i> [70], 2009	Hongkong	22	0	20	63.6	31.8	NR
Wang <i>et al</i> [71], 2010	China	125	125	24	30.4	NR	NR
Kuo <i>et al</i> [72], 2010	Taiwan	124	0	> 12	66.1	66.1	NR
Cai <i>et al</i> [73], 2010	China	11	0	22	42.8	0	NR
Liu <i>et al</i> [74], 2011	China	61	61	15	50.8	45.9	8/61
Jung <i>et al</i> [75], 2011	South Korea	19	9	12	31.6	21	0
Chan <i>et al</i> [76], 2011	Hongkong	53	53	47	69.8	NR	9/53
Liang <i>et al</i> [77], 2011	Hongkong	84	43		44	14.3	NR
Chaung <i>et al</i> [78], 2012	United States	39	0	14	89.7	38.5	0
Hadziyannis <i>et al</i> [15], 2012	Greece	33	33	69	45.4	45.4	13/33
Ha <i>et al</i> [79], 2012	China	145	145	16	65.5	64.1	NR
Song <i>et al</i> [80], 2012	South Korea	48	0	18	41.6	NR	NR
He <i>et al</i> [81], 2013	China	66	66	17	28.8	NR	2/66
Kim <i>et al</i> [82], 2013	Korea	45	45	26	73.3	53.3	NR
Jeng <i>et al</i> [83], 2013	Taiwan	95	95	> 12	57.9	45.3	0/95
Kwon <i>et al</i> [84], 2013	South Korea	16	NR	32	25	25	2/16
Ridruejo <i>et al</i> [85], 2014	Argentina	35	0	15	25.7	NR	18/35
Sohn <i>et al</i> [86], 2014	South Korea	95	54	22	83.1	NR	0/95
Patwardhan <i>et al</i> [87], 2014	United States	33	33	36	63.6	48.5	0/33
He <i>et al</i> [88], 2014	China	97	0	32	8.2	1	11/97
Chen <i>et al</i> [40], 2014	Taiwan	188	105	49	66.5	NR	33/185
Jiang <i>et al</i> [89], 2015	China	72	39	13	65.3	41.7	NR
Seto <i>et al</i> [90], 2015	Hongkong	184	184	12	91.8	22.8	0
Peng <i>et al</i> [91], 2015	China	65	21	12	43.1	27.7	1/65
Jeng <i>et al</i> [92], 2016	Taiwan	85	85	155	69	52	2/85
Qiu <i>et al</i> [93], 2016	China	112	0	52	48.2	NR	1/112
Yao <i>et al</i> [94], 2017	Taiwan	119	119	6 yr	25.2	12.7	44/119 <sup>2</sup>
Cao <i>et al</i> [95], 2017	China	82	22	91	70.7	34.1	5/82
Chen <i>et al</i> [96], 2018	Taiwan	143	104	104	67.1	48.9	7/143
Hung <i>et al</i> [97], 2017	Taiwan	73	73	6 yr	54.8	6.8	20/73
Berg <i>et al</i> [42], 2017	German	21	21	144	52	23	4/21
Jeng <i>et al</i> [33], 2018	Taiwan	691	691	6 yr	79.2	60.6	42/691
Liem <i>et al</i> [39], 2019	Canada	45	27	72	71	13	1/45
Kaewdech <i>et al</i> [12], 2020	Thailand	92	70	48	63	33.7	2/92

<sup>1</sup>Not reported.<sup>2</sup>All patients had hepatitis B surface antigen level < 200 IU/mL at the end of treatment.

EOT: End of treatment; HBsAg: Hepatitis B surface antigen; NR: Not reported.

**Table 3 Factors predictive of hepatitis B virus relapse**

Baseline at pretreatment	On-treatment	End of treatment
<b>Virological relapse</b>		
High age[40,44]	Short consolidation duration[38]	High HBsAg level[40,41]
Male sex[40]		High HBcrAg level[12]
High HBsAg level[44]		High HBV RNA level[12]
<b>Clinical relapse</b>		
High HBsAg level[44]	Short consolidation duration[44]	High HBsAg level[13,40,41]
		High HBcrAg level[12,13,52]
		High HBV RNA level[12,52]

HBcrAg: Hepatitis B core-related antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

**Table 4 Factors predictive of hepatitis B surface antigen clearance**

Baseline at pretreatment	On-treatment	End of treatment
Low ALT level[40]	Long treatment duration[40]	Low HBsAg level especially < 100 IU/mL[41]
Low HBV DNA level[40]	HBsAg level reduction > 1 log <sub>10</sub> IU/mL[33]	Low HBcrAg level[13]

ALT: Alanine aminotransferase; HBcrAg: Hepatitis B core-related antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

was the optimal cutoff[41] to predict low rates of HBV relapse and a high chance of HBsAg loss. A meta-analysis involving 1573 patients found that the same EOT HBsAg level (> 100 IU/mL) was associated with an increased risk of VR and CR, however, it is not predictive of CR in a subgroup of Asian patients[44]. The finding is consistent with our study in Thai patients in which the HBsAg level was not associated with the development of CR. A recent multicenter study by Sonneveld *et al*[13] found that a cutoff level of < 50 IU/mL was the best for predicting a sustained response and HBsAg loss[13]. In conclusion, HBsAg level is a good predictor of HBsAg loss after NA cessation, but its use as a biomarker to predict CR, especially in Asian patients, is still not clear.

### HBcrAg level

Serum HBcrAg has emerged as a novel biomarker in CHB patients. Serum HBcrAg measurement is the combined assay of hepatitis B core antigen, HBeAg, and p22 protein, and it has been shown to be a potential surrogate marker of intrahepatic cccDNA[45,46]. In previous Japanese reports, an increased HBcrAg level was associated with an increase in the rate of off-therapy relapse in NA-treated patients[47]. In addition, a multicenter cohort of Taiwanese patients showed that HBcrAg and HBsAg measured at the time of NA discontinuation were predictive of off-therapy relapse[48]. Moreover, data from CREATE project, a multicenter study including both Asian and Caucasian patients, confirmed the utility of serum HBcrAg. The low cutoff of < 2 log<sub>10</sub> U/mL was associated with sustained response and HBsAg clearance regardless of HBeAg status and ethnicity[13]. A compilation of the clinical applications of HBcrAg in the cessation of NA is shown in Table 5.

### HBV RNA level

Serum HBV RNA is closely associated with the transcriptional activity of intrahepatic cccDNA and can be quantified by polymerase chain reaction-based techniques[31]. Moreover, this novel marker is potentially valuable in monitoring for relapse after NA

**Table 5** Hepatitis B core-related antigen level and clinical application

Ref.	n (%)	End of treatment HBcrAg level (log <sub>10</sub> U/mL)	Clinical application
Shinkai <i>et al</i> [98], 2006	22	< 3.4	Predictive factor for absence of the off-therapy relapse
Matsumoto <i>et al</i> [47], 2007	34	< 3.2	Predictive factor for absence of the off-therapy relapse
Jung <i>et al</i> [99], 2016	113	≤ 3.7	Virological relapse within 1 yr of NA cessation
Hsu <i>et al</i> [48], 2019	135	NR	Predictive factors of HBsAg loss and lower clinical relapse
Kaewdech <i>et al</i> [12], 2020	92	< 3	Low risk of off-therapy relapse
Papatheodoridi <i>et al</i> [54], 2020	57	< 2	Predictive factor of HBsAg loss, not required retreatment
Sonneveld <i>et al</i> [13], 2020	572	< 2	Higher risk of sustained response and HBsAg loss

ALT: Alanine aminotransferase; HBcrAg: Hepatitis B core-related antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; NA: Nucleos(t)ide analog; NR: Not reported.

discontinuation[49]. A study by Wang *et al*[49] reported that viral rebound occurred in 100% of patients who had detectable HBV RNA at EOT[49]. A recent study in HBeAg-positive patients found that positive serum HBV RNA at EOT was associated with the development of off-therapy CR[50].

### The combination of biomarkers

Together, the data suggest that serum qHBsAg, HBcrAg, and HBV RNA, especially at EOT, are predictive of the outcomes following NA cessation. A few studies have explored the usefulness of combining the biomarkers to select the best candidates for stopping NA[12,48,51,52]. A post-hoc analysis from China included 130 CHB patients who discontinued NA and serial followed-up HBV DNA, qHBsAg and HBV RNA[50] found that the combination of negative HBV DNA and HBV RNA at EOT correlated with lower a CR rate and had an excellent 92% negative predictive value (NPV). Another study, combining qHBsAg, and HBcrAg reported that lower qHBsAg, and HBcrAg levels were associated with lower CR and increased HBsAg clearance[48]. Furthermore, a combination of the two biomarkers before stopping NA showed that no patients with negative HBV RNA, and HBcrAg < 4 log<sub>10</sub> U/mL at EOT developed CR[52]. The result is consistent with that observed in our study of the combination of the three biomarkers, *i.e.* qHBsAg, HBcrAg, and HBV RNA in the prediction of CR after cessation of NA. We found that HBcrAg of < 3 log<sub>10</sub> U/mL and HBV RNA of < 2 log<sub>10</sub> U/mL had 100% NPV for CR[12]. Nonetheless, when combining all three biomarkers, the prediction of CR was not better than that with HBcrAg plus HBV RNA [12].

## SCORING SYSTEMS TO PREDICT HBV RELAPSE AND HBsAg CLEARANCE

Apart from using only biomarkers, previous studies illustrated that other clinical and laboratory parameters were significantly associated with post off-treatment outcomes. Therefore, the development of scoring systems utilizing various variables to predict HBV relapse and HBsAg clearance is foreseeable. The first score to predict CR after NA discontinuation is the Japan society of hepatology (JSH) score that consisted of the HBsAg level and HBcrAg level at the time of cessation. The JSH scores are divided into low, moderate, and high-risk groups for HBV relapse after NA cessation[53]. However, this predictive score is not widely used outside the country of origin.

The SCALE-B scoring system was developed using data from 135 Taiwanese CHB patients[48]. The score is comprised of the HBsAg level (S), HBcrAg (C), age (A), ALT (L), and tenofovir (E) for HBV (B) and is calculated as HBsAg (log<sub>10</sub> IU/mL) + 20 × HBcrAg (log<sub>10</sub> U/mL) + 2 × age (yr) + ALT (U/L) + 40 for the use of tenofovir. The scores are divided into three strata, low (< 260 points), intermediate (260-320 points), and high (> 320 points) risk of CR. A score of < 260 points was associated with a subsequent HBsAg loss in 27.1% of the patients at 3 years[48]. The SCALE-B score has

been validated in a Caucasian population in which it predicted HBsAg clearance, but not relapse[54]. Recently, the CREATE study, which included a large number of Asian as well as Caucasian patients reported that the SCALE-B score predicted CR and HBsAg loss regardless of HBeAg status or ethnicity[13].

## IMMUNE SYSTEM EFFECTS AFTER DISCONTINUATION OF ANTIVIRAL AGENTS

T cells contribute to the control of HBV infection by killing infected hepatocytes[55]. However, chronic HBV infection can exhaust immune activity, particularly T cell function[55], as the longer time of HBV infection is associated with the length of exposure to high antigenicity[56]. With NA therapy, T cell function decreases over time. With discontinuation of NA, T cell function may recover with the increase in the number of active T cells and less exhausted phenotypes[57,58].

After the cessation of NA treatment, the HBV DNA usually becomes detectable and often triggers ALT flares that reflect the immune response. Increased numbers of HBV-specific T cells were observed in patients in virological remission after NA discontinuation[59]. A study by Rinker *et al*[58] that high function of HBV-specific T cells was observed after NA cessation in patients with subsequent HBsAg loss, especially HBV-specific CD4<sup>+</sup> T cells[58]. In addition, T cell function increased after programmed death-ligand 1 blockage. More recently, a study by a Spanish group[60] reported that an HBsAg level of  $\leq 1000$  IU/mL, lower cccDNA transcriptional activity, and a higher HBV-specific T cell response were associated with the development of HBsAg loss.

A new concept of the immune response after NA cessation, beneficial flare *vs* bad flare is of interest, and was introduced by a Taiwanese group[61]. HBsAg kinetics may be useful in predicting whether patients will require retreatment after CR. Initiation of retreatment is considered in patients who have an increase in HBsAg level before or during ALT flare, which reflects an ineffective immune response. On the other hand, patients in whom a reduction on the HBsAg level was observed before or during ALT flare may not need retreatment, and spontaneous HBsAg clearance may eventually occur[62].

## MONITORING /RESTARTING THERAPY AFTER STOPPING ANTIVIRAL AGENT THERAPY

At present, there is no consensus on how to monitor and when to restart NA therapy. Previous studies reported that most HBV relapses occurred within 1 year after the discontinuation of antiviral agents. Most studies recommend careful monitoring, with physical examinations, liver function tests, and serum HBV DNA assays every 1-2 mo for the first 3 mo, every 3 mo for 1 year, and every 6 mo thereafter[12-14,63]. If the patient experiences ALT flare, then close follow-up every week with liver function tests and PT are mandatory for deciding whether prompt retreatment is needed.

Currently, retreatment criteria differ among the studies summarized in Table 6[12, 13,39,63]. Most suggested that retreatment should be initiated in patients with an ALT level  $> 10$  times above the ULN regardless of bilirubin level, with an ALT level  $> 5$  times above ULN plus a bilirubin  $> 1.5$ -2 mg/dL, persistent of ALT level  $> 5$  times the ULN for 4 wk, or an ALT elevation with either a prolonged PT  $> 2$  sec or a bilirubin level  $> 1.5$ -2 mg/dL. The retreatment strategy is challenging as CR may reflect the immune restoration and reintroduction of NA might alleviate the effect. However, delayed initiation of retreatment can cause severe ALT flare, and eventually liver decompensation. The biomarkers or tools to aid justification of the optimal timing of retreatment are unmet needs.

## PERSPECTIVE OF NA DISCONTINUATION IN EASTERN AND WESTERN COUNTRIES

In Asian and Caucasian populations, there are differences in rates of HBsAg clearance and HBV relapse. Caucasians have a higher probability of achieving a functional cure after NA cessation[13]. HBsAg clearance has been observed in 19%-29% of Caucasians at 2 years[42,64] whereas it had been found in only 1.78%/year in Asians. This



**Table 6 Summary of follow-up interval and retreatment criteria**

Ref.	Follow-up interval	Criteria of retreatment
Berg <i>et al</i> [42], 2017	Every 2 wk in the first 3 mo, every 4 wk until week 48, and every 12 wk thereafter until week 144	Two consecutive total bilirubin > 1.5 mg/dL plus ALT > ULN  Two consecutive PT $\geq$ 2.0 seconds (INR $\geq$ 0.5) prolonged from baseline with adequate vitamin K therapy plus ALT > ULN  Two consecutive ALT > 10 $\times$ ULN  ALT > 2 $\times$ but $\leq$ 5 $\times$ ULN persisting for $\geq$ 12 wk plus HBV DNA > 20000 copies/mL  ALT 5 $\times$ but $\leq$ 10 $\times$ ULN persisting for $\geq$ 4 wk
Papatheodoridi <i>et al</i> [63], 2018	Every mo in the first 3 mo then at least every 3 mo until month 12	Greece cohort: (1) ALT > 10 $\times$ ULN; (2) ALT > 5 $\times$ ULN plus total bilirubin > 2 mg/dL; (3) ALT > 3 $\times$ ULN plus HBV DNA > 100000 IU/mL; and (4) ALT > ULN plus HBV DNA > 2000 IU/mL on three sequential occasions  Taiwanese cohort: (1) ALT > 2 $\times$ ULN twice 3 mo apart plus HBV DNA > 2000 IU/mL; (2) Total bilirubin > 2 mg/dL; and (3) PT $\geq$ 3 seconds of control range
Liem <i>et al</i> [39], 2019	Wk 4, 6, 12, 18, 24, 36, 48, 60, and 72	HBeAg seroreversion  HBV DNA > 2000 IU/mL plus ALT > 600 IU/mL  HBV DNA > 2000 IU/mL plus ALT > 5 $\times$ ULN (40 IU/mL) on two consecutive visits  HBV DNA > 2000 IU/mL plus ALT > 200 IU/mL but < 600 IU/mL for > 6–8 wk  HBV DNA > 20000 IU/mL on two consecutive visits at least 4 wk apart
García-López <i>et al</i> [60], 2020	Monthly in the first 6 mo then every 3–4 mo until 24 mo	Two consecutive ALT > 10 $\times$ ULN regardless of HBV DNA level  ALT > 5–10 $\times$ ULN and HBV DNA > 2000 IU/mL persisting for $\geq$ 4 wk  ALT > 2–5 $\times$ ULN and HBV DNA > 2000 IU/mL persisting for $\geq$ 6 mo  Need for immunosuppressive treatment

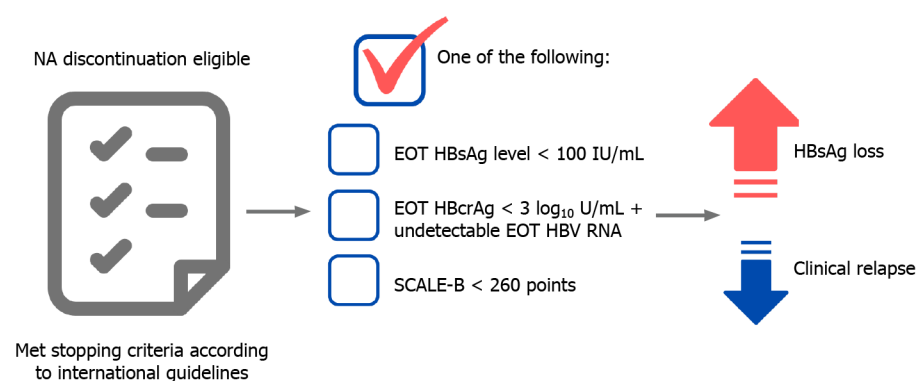
ALT: Alanine aminotransferase; HBeAg: Hepatitis B e antigen; HBV: hepatitis B virus; INR: International normalized ratio; PT: Prothrombin time; ULN: Upper limit of normal.

phenomenon might be explained by the difference of HBV genotypes between Asians and Caucasians, and the duration of infectivity. In Asians, the most common genotypes are B and C, in contrast to the Caucasians in which genotype D is more common[65]. Regarding the duration of infection, most Asian CHB patients are infected perinatally, resulting in a longer extent of chronic infection than in Caucasian patients[66]. Therefore, apart from the chance of patients to have drug-free periods, lower long-term side effects and costs, the ultimate benefit of achieving a functional cure after NA cessation is lower in Asians than in Caucasians.

Another discrepancy between East and West is the consideration of stopping NA in cirrhotic patients. The APASL recommends that in highly selected cirrhotic patients, NA discontinuation may be considered according to the stopping criteria and safety results of previous Asian studies[11,33]. On the contrary, the AASLD and EASL do not recommend NA cessation in cirrhotic patients because safety concerns[9,10].

## CONCLUSION

From our perspective, the stop strategy is optimal in highly selected noncirrhotic CHB patients. At present, we propose the ideal candidates for NA discontinuation in CHB patients as shown in Figure 2. The major benefit of this strategy is it enhances the chance of achieving a functional cure faster than continuous long-term NA therapy. However, there are some caveats, including severe CR, liver decompensation, or HCC development to be considered. The current unmet needs for NA discontinuation strategy in CHB patients are the better prediction of the patients who are good candidates for stopping, emerging and more widely available noninvasive biomarkers, and the identification of the best timing to consider retreatment initiation, balancing the chance of achieving functional cure and liver decompensation.



**Figure 2 Proposed ideal candidates to for stopping the use of antiviral agents in chronic hepatitis B patients.** EOT: End of treatment; HBcrAg: Hepatitis B core-related antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

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## REFERENCES

- Polaris Observatory Collaborators.** Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol* 2018; **3**: 383-403 [PMID: 29599078 DOI: 10.1016/S2468-1253(18)30056-6]
- Ganem D, Prince AM.** Hepatitis B virus infection--natural history and clinical consequences. *N Engl J Med* 2004; **350**: 1118-1129 [PMID: 15014185 DOI: 10.1056/NEJMra031087]
- Udompap P, Tanwandee T, Gani R.** Affordability of Antiviral Therapy in Asia-Pacific Countries and Its Impact on Public Health Outcomes. *Clin Liver Dis (Hoboken)* 2020; **16**: 249-253 [PMID: 33489097 DOI: 10.1002/cld.977]
- Kumar R, Pérez-Del-Pulgar S, Testoni B, Lebossé F, Zoulim F.** Clinical relevance of the study of hepatitis B virus covalently closed circular DNA. *Liver Int* 2016; **36** Suppl 1: 72-77 [PMID: 26725901 DOI: 10.1111/liv.13001]
- Nassal M.** HBV cccDNA: viral persistence reservoir and key obstacle for a cure of chronic hepatitis B. *Gut* 2015; **64**: 1972-1984 [PMID: 26048673 DOI: 10.1136/gutjnl-2015-309809]
- Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, Washington MK, Germanidis G, Flaherty JF, Aguilar Schall R, Bornstein JD, Kitrinis KM, Subramanian GM, McHutchison JG, Heathcote EJ.** Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet* 2013; **381**: 468-475 [PMID: 23234725 DOI: 10.1016/S0140-6736(12)61425-1]
- Lok AS, McMahon BJ, Brown RS Jr, Wong JB, Ahmed AT, Farah W, Almasri J, Alahdab F, Benkhadra K, Mouchli MA, Singh S, Mohamed EA, Abu Dabrh AM, Prokop LJ, Wang Z, Murad MH, Mohammed K.** Antiviral therapy for chronic hepatitis B viral infection in adults: A systematic review and meta-analysis. *Hepatology* 2016; **63**: 284-306 [PMID: 26566246 DOI: 10.1002/hep.28280]
- Papathodoridis G, Vlachogiannakos I, Cholongitas E, Wurstthorn 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]
- 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]
- 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]
- 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]
- Kaewdech A, Tangkijvanich P, Sripongpun P, Witeerungrot T, Jandee S, Tanaka Y, Piratvisuth T.** Hepatitis B surface antigen, core-related antigen and HBV RNA: Predicting clinical relapse after NA

- therapy discontinuation. *Liver Int* 2020; **40**: 2961-2971 [PMID: [32668074](#) DOI: [10.1111/liv.14606](#)]
- 13 **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 Siederdisen 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](#)]
  - 14 **Chevaliez S**, Hézode C, Bahrami S, Grare M, Pawlotsky JM. Long-term hepatitis B surface antigen (HBsAg) kinetics during nucleoside/nucleotide analogue therapy: finite treatment duration unlikely. *J Hepatol* 2013; **58**: 676-683 [PMID: [23219442](#) DOI: [10.1016/j.jhep.2012.11.039](#)]
  - 15 **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](#)]
  - 16 **Lok AS**, Zoulim F, Dusheiko G, Chan HLY, Buti M, Ghany MG, Gaggar A, Yang JC, Wu G, Flaherty JF, Subramanian GM, Locarnini S, Marcellin P. Durability of Hepatitis B Surface Antigen Loss With Nucleotide Analogue and Peginterferon Therapy in Patients With Chronic Hepatitis B. *Hepatol Commun* 2020; **4**: 8-20 [PMID: [31909352](#) DOI: [10.1002/hep4.1436](#)]
  - 17 **Brunetto MR**, Bonino F. Interferon therapy of chronic hepatitis B. *Intervirology* 2014; **57**: 163-170 [PMID: [25034484](#) DOI: [10.1159/000360941](#)]
  - 18 **Liaw YF**, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, Guan R, Lau GK, Locarnini S; Chronic Hepatitis B Guideline Working Party of the Asian-Pacific Association for the Study of the Liver. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. *Hepatol Int* 2008; **2**: 263-283 [PMID: [19669255](#) DOI: [10.1007/s12072-008-9080-3](#)]
  - 19 **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](#)]
  - 20 **Chotiayaputta W**, Peterson C, Ditah FA, Goodwin D, Lok AS. Persistence and adherence to nucleos(t)ide analogue treatment for chronic hepatitis B. *J Hepatol* 2011; **54**: 12-18 [PMID: [20888661](#) DOI: [10.1016/j.jhep.2010.06.016](#)]
  - 21 **Thompson AJ**, Ayres A, Yuen L, Bartholomeusz A, Bowden DS, Iser DM, Chen RY, Demediuk B, Shaw G, Bell SJ, Watson KJ, Locarnini SA, Desmond PV. Lamivudine resistance in patients with chronic hepatitis B: role of clinical and virological factors. *J Gastroenterol Hepatol* 2007; **22**: 1078-1085 [PMID: [17608854](#) DOI: [10.1111/j.1440-1746.2006.04630.x](#)]
  - 22 **Ford N**, Scourse R, Lemoine M, Hutin Y, Bulterys M, Shubber Z, Donchuk D, Wandeler G. Adherence to Nucleos(t)ide Analogue Therapies for Chronic Hepatitis B Infection: A Systematic Review and Meta-Analysis. *Hepatol Commun* 2018; **2**: 1160-1167 [PMID: [30288470](#) DOI: [10.1002/hep4.1247](#)]
  - 23 **Allard N**, Dev A, Dwyer J, Srivatsa G, Thompson A, Cowie B. Factors associated with poor adherence to antiviral treatment for hepatitis B. *J Viral Hepat* 2017; **24**: 53-58 [PMID: [27502689](#) DOI: [10.1111/jvh.12582](#)]
  - 24 **Lievelde FI**, van Vlerken LG, Siersema PD, van Erpecum KJ. Patient adherence to antiviral treatment for chronic hepatitis B and C: a systematic review. *Ann Hepatol* 2013; **12**: 380-391 [PMID: [23619254](#) DOI: [10.1016/S1665-2681\(19\)31000-2](#)]
  - 25 **Berg T**, Marcellin P, Zoulim F, Moller B, Trinh H, Chan S, Suarez E, Lavocat F, Snow-Lampart A, Frederick D, Sorbel J, Borroto-Esoda K, Oldach D, Rousseau F. Tenofovir is effective alone or with emtricitabine in adefovir-treated patients with chronic-hepatitis B virus infection. *Gastroenterology* 2010; **139**: 1207-1217 [PMID: [20600025](#) DOI: [10.1053/j.gastro.2010.06.053](#)]
  - 26 **de Fraga RS**, Van Vaisberg V, Mendes LCA, Carrilho FJ, Ono SK. Adverse events of nucleos(t)ide analogues for chronic hepatitis B: a systematic review. *J Gastroenterol* 2020; **55**: 496-514 [PMID: [32185517](#) DOI: [10.1007/s00535-020-01680-0](#)]
  - 27 **Udompap P**, Kim D, Ahmed A, Kim WR. Longitudinal trends in renal function in chronic hepatitis B patients receiving oral antiviral treatment. *Aliment Pharmacol Ther* 2018; **48**: 1282-1289 [PMID: [30370967](#) DOI: [10.1111/apt.15020](#)]
  - 28 **Buti M**, Gane E, Seto WK, Chan HL, Chuang WL, Stepanova T, Hui AJ, Lim YS, Mehta R, Janssen HL, Acharya SK, Flaherty JF, Massetto B, Cathcart AL, Kim K, Gaggar A, Subramanian GM, McHutchison JG, Pan CQ, Brunetto M, Izumi N, Marcellin P; GS-US-320-0108 Investigators. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol* 2016; **1**: 196-206 [PMID: [28404092](#) DOI: [10.1016/S2468-1253\(16\)30107-8](#)]
  - 29 **Chan HL**, Fung S, Seto WK, Chuang WL, Chen CY, Kim HJ, Hui AJ, Janssen HL, Chowdhury A, Tsang TY, Mehta R, Gane E, Flaherty JF, Massetto B, Gaggar A, Kitrinos KM, Lin L, Subramanian GM, McHutchison JG, Lim YS, Acharya SK, Agarwal K; GS-US-320-0110 Investigators. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol* 2016; **1**: 185-195 [PMID: [28404091](#) DOI: [10.1016/S2468-1253\(16\)30024-3](#)]
  - 30 **Agarwal K**, Brunetto M, Seto WK, Lim YS, Fung S, Marcellin P, Ahn SH, Izumi N, Chuang WL, Bae H, Sharma M, Janssen HLA, Pan CQ, Çelen MK, Furusyo N, Shalimar D, Yoon KT, Trinh H, Flaherty JF, Gaggar A, Lau AH, Cathcart AL, Lin L, Bhardwaj N, Suri V, Mani Subramanian G,

- Gane EJ, Buti M, Chan HLY; GS-US-320-0110; GS-US-320-0108 Investigators. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. *J Hepatol* 2018; **68**: 672-681 [PMID: [29756595](#) DOI: [10.1016/j.jhep.2017.11.039](#)]
- 31 **Lim SG**, Aung MO, Chung SW, Soon CS, Mak BH, Lee KH. Patient preferences for hepatitis B therapy. *Antivir Ther* 2013; **18**: 663-670 [PMID: [23232291](#) DOI: [10.3851/IMP2482](#)]
- 32 **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](#)]
- 33 **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](#)]
- 34 **Kuo MT**, Hu TH, Hung CH, Wang JH, Lu SN, Tsai KL, Chen CH. Hepatitis B virus relapse rates in chronic hepatitis B patients who discontinue either entecavir or tenofovir. *Aliment Pharmacol Ther* 2019; **49**: 218-228 [PMID: [30484881](#) DOI: [10.1111/apt.15053](#)]
- 35 **Ma TL**, Hu TH, Hung CH, Wang JH, Lu SN, Chen CH. Incidence and predictors of retreatment in chronic hepatitis B patients after discontinuation of entecavir or tenofovir treatment. *PLoS One* 2019; **14**: e0222221 [PMID: [31584951](#) DOI: [10.1371/journal.pone.0222221](#)]
- 36 **Ahn J**, Lee HM, Lim JK, Pan CQ, Nguyen MH, Ray Kim W, Mannalithara A, Trinh H, Chu D, Tran T, Min A, Do S, Te H, Reddy KR, Lok AS. Entecavir safety and effectiveness in a national cohort of treatment-naïve chronic hepatitis B patients in the US - the ENUMERATE study. *Aliment Pharmacol Ther* 2016; **43**: 134-144 [PMID: [26510638](#) DOI: [10.1111/apt.13440](#)]
- 37 **Yip TC**, Wong VW, Chan HL, Tse YK, Lui GC, Wong GL. Tenofovir Is Associated With Lower Risk of Hepatocellular Carcinoma Than Entecavir in Patients With Chronic HBV Infection in China. *Gastroenterology* 2020; **158**: 215-225.e6 [PMID: [31574268](#) DOI: [10.1053/j.gastro.2019.09.025](#)]
- 38 **Chi H**, Hansen BE, Yim C, Arends P, Abu-Amara M, van der Eijk AA, Feld JJ, de Kneegt 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](#)]
- 39 **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](#)]
- 40 **Chen CH**, Lu SN, Hung CH, Wang JH, Hu TH, Changchien CS, Lee CM. The role of hepatitis B surface antigen quantification in predicting HBsAg loss and HBV relapse after discontinuation of lamivudine treatment. *J Hepatol* 2014; **61**: 515-522 [PMID: [24798617](#) DOI: [10.1016/j.jhep.2014.04.029](#)]
- 41 **Liu J**, Li T, Zhang L, Xu A. The Role of Hepatitis B Surface Antigen in Nucleos(t)ide Analogues Cessation Among Asian Patients With Chronic Hepatitis B: A Systematic Review. *Hepatology* 2019; **70**: 1045-1055 [PMID: [30561829](#) DOI: [10.1002/hep.30474](#)]
- 42 **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](#)]
- 43 **Mak LY**, Seto WK, Fung J, Yuen MF. Use of HBsAg quantification in the natural history and treatment of chronic hepatitis B. *Hepatology* 2020; **14**: 35-46 [PMID: [31745711](#) DOI: [10.1007/s12072-019-09998-5](#)]
- 44 **Liu Y**, Jia M, Wu S, Jiang W, Feng Y. Predictors of relapse after cessation of nucleos(t)ide analog treatment in HBeAg-negative chronic hepatitis B patients: A meta-analysis. *Int J Infect Dis* 2019; **86**: 201-207 [PMID: [31394205](#) DOI: [10.1016/j.ijid.2019.07.036](#)]
- 45 **Mak LY**, Wong DK, Cheung KS, Seto WK, Lai CL, Yuen MF. Review article: hepatitis B core-related antigen (HBcrAg): an emerging marker for chronic hepatitis B virus infection. *Aliment Pharmacol Ther* 2018; **47**: 43-54 [PMID: [29035003](#) DOI: [10.1111/apt.14376](#)]
- 46 **Testoni B**, Lebossé F, Scholtes C, Berby F, Miaglia C, Subic M, Loglio A, Facchetti F, Lampertico P, Levrero M, Zoulim F. Serum hepatitis B core-related antigen (HBcrAg) correlates with covalently closed circular DNA transcriptional activity in chronic hepatitis B patients. *J Hepatol* 2019; **70**: 615-625 [PMID: [30529504](#) DOI: [10.1016/j.jhep.2018.11.030](#)]
- 47 **Matsumoto A**, Tanaka E, Minami M, Okanoue T, Yatsuhashi H, Nagaoka S, Suzuki F, Kobayashi M, Chayama K, Imamura M, Yotsuyanagi H, Nakaoka S, Maki N, Kawata S, Kumada H, Iino S, Kiyosawa K. Low serum level of hepatitis B core-related antigen indicates unlikely reactivation of hepatitis after cessation of lamivudine therapy. *Hepatology* 2007; **37**: 661-666 [PMID: [17584261](#) DOI: [10.1111/j.1872-034X.2007.00094.x](#)]
- 48 **Hsu YC**, Nguyen MH, Mo LR, Wu MS, Yang TH, Chen CC, Tseng CH, Tai CM, Wu CY, Lin JT, Tanaka Y, Chang CY. Combining hepatitis B core-related and surface antigens at end of nucleos(t)ide analogue treatment to predict off-therapy relapse risk. *Aliment Pharmacol Ther* 2019; **49**: 107-115 [PMID: [30450681](#) DOI: [10.1111/apt.15058](#)]
- 49 **Wang J**, Shen T, Huang X, Kumar GR, Chen X, Zeng Z, Zhang R, Chen R, Li T, Zhang T, Yuan Q,

- Li PC, Huang Q, Colonna R, Jia J, Hou J, McCrae MA, Gao Z, Ren H, Xia N, Zhuang H, Lu F. Serum hepatitis B virus RNA is encapsidated pregenome RNA that may be associated with persistence of viral infection and rebound. *J Hepatol* 2016; **65**: 700-710 [PMID: [27245431](#) DOI: [10.1016/j.jhep.2016.05.029](#)]
- 50 **Fan R**, Zhou B, Xu M, Tan D, Niu J, Wang H, Ren H, Chen X, Wang M, Ning Q, Shi G, Sheng J, Tang H, Bai X, Liu S, Lu F, Peng J, Sun J, Xie Q, Hou J; Chronic Hepatitis B Study Consortium. Association Between Negative Results From Tests for HBV DNA and RNA and Durability of Response After Discontinuation of Nucleos(t)ide Analogue Therapy. *Clin Gastroenterol Hepatol* 2020; **18**: 719-727.e7 [PMID: [31362119](#) DOI: [10.1016/j.cgh.2019.07.046](#)]
- 51 **Carey I**, Gersch J, Wang B, Moigboi C, Kuhns M, Cloherty G, Dusheiko G, Agarwal K. Pregenomic HBV RNA and Hepatitis B Core-Related Antigen Predict Outcomes in Hepatitis B e Antigen-Negative Chronic Hepatitis B Patients Suppressed on Nucleos(T)ide Analogue Therapy. *Hepatology* 2020; **72**: 42-57 [PMID: [31701544](#) DOI: [10.1002/hep.31026](#)]
- 52 **Fan R**, Peng J, Xie Q, Tan D, Xu M, Niu J, Wang H, Ren H, Chen X, Wang M, Sheng J, Tang H, Bai X, Wu Y, Zhou B, Sun J, Hou J; Chronic Hepatitis B Study Consortium. Combining Hepatitis B Virus RNA and Hepatitis B Core-Related Antigen: Guidance for Safely Stopping Nucleos(t)ide Analogues in Hepatitis B e Antigen-Positive Patients With Chronic Hepatitis B. *J Infect Dis* 2020; **222**: 611-618 [PMID: [32211776](#) DOI: [10.1093/infdis/jiaa136](#)]
- 53 **Drafting Committee for Hepatitis Management Guidelines and the Japan Society of Hepatology**. JSH Guidelines for the Management of Hepatitis B Virus Infection. *Hepatol Res* 2014; **44** Suppl S1: 1-58 [PMID: [24397839](#) DOI: [10.1111/hepr.12269](#)]
- 54 **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](#)]
- 55 **Boni C**, Laccabue D, Lampertico P, Giuberti T, Viganò M, Schivazappa S, Alfieri A, Pesci M, Gaeta GB, Brancaccio G, Colombo M, Missale G, Ferrari C. Restored function of HBV-specific T cells after long-term effective therapy with nucleos(t)ide analogues. *Gastroenterology* 2012; **143**: 963-73.e9 [PMID: [22796241](#) DOI: [10.1053/j.gastro.2012.07.014](#)]
- 56 **Boni C**, Fiscaro P, Valdatta C, Amadei B, Di Vincenzo P, Giuberti T, Laccabue D, Zerbini A, Cavalli A, Missale G, Bertolotti A, Ferrari C. Characterization of hepatitis B virus (HBV)-specific T-cell dysfunction in chronic HBV infection. *J Virol* 2007; **81**: 4215-4225 [PMID: [17287266](#) DOI: [10.1128/JVI.02844-06](#)]
- 57 **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](#)]
- 58 **Rinker F**, Zimmer CL, Höner Zu Siederdissen C, Manns MP, Kraft AR, Wedemeyer H, Björkström NK, Cornberg M. Hepatitis B virus-specific T cell responses after stopping nucleos(t)ide analogue therapy in HBeAg-negative chronic hepatitis B. *J Hepatol* 2018; **69**: 584-593 [PMID: [29758333](#) DOI: [10.1016/j.jhep.2018.05.004](#)]
- 59 **Rivino L**, Le Bert N, Gill US, Kunasegaran K, Cheng Y, Tan DZ, Becht E, Hansi NK, Foster GR, Su TH, Tseng TC, Lim SG, Kao JH, Newell EW, Kennedy PT, Bertolotti A. Hepatitis B virus-specific T cells associate with viral control upon nucleos(t)ide-analogue therapy discontinuation. *J Clin Invest* 2018; **128**: 668-681 [PMID: [29309050](#) DOI: [10.1172/JCI92812](#)]
- 60 **García-López M**, Lens S, Pallott LJ, Testoni B, Rodríguez-Tajes S, Mariño Z, Bartres C, García-Pras E, Leonel T, Perpiñán E, Lozano JJ, Rodríguez-Frías F, Koutsoudakis G, Zoulim F, Maini MK, Forns X, Pérez-Del-Pulgar S. Viral and immune factors associated with successful treatment withdrawal in HBeAg-negative chronic hepatitis B patients. *J Hepatol* 2021; **74**: 1064-1074 [PMID: [33278456](#) DOI: [10.1016/j.jhep.2020.11.043](#)]
- 61 **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](#)]
- 62 **Jeng WJ**, Chang ML, Liaw YF. Off-therapy precipitous HBsAg decline predicts HBsAg loss after finite entecavir therapy in HBeAg-negative patients. *J Viral Hepat* 2019; **26**: 1019-1026 [PMID: [31009126](#) DOI: [10.1111/jvh.13114](#)]
- 63 **Papatheodoridis GV**, Manolakopoulos S, Su TH, Siakavellas S, Liu CJ, Kourikou A, Yang HC, Kao JH. Significance of definitions of relapse after discontinuation of oral antivirals in HBeAg-negative chronic hepatitis B. *Hepatology* 2018; **68**: 415-424 [PMID: [28859219](#) DOI: [10.1002/hep.29497](#)]
- 64 **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](#)]
- 65 **Tangkijvanich P**, Mahachai V, Komolmit P, Fongsarun J, Theamboonlers A, Poovorawan Y. Hepatitis B virus genotypes and hepatocellular carcinoma in Thailand. *World J Gastroenterol* 2005; **11**: 2238-2243 [PMID: [15818732](#) DOI: [10.3748/wjg.v11.i15.2238](#)]
- 66 **Chamroonkul N**, Piratvisuth T. Hepatitis B During Pregnancy in Endemic Areas: Screening,



- Treatment, and Prevention of Mother-to-Child Transmission. *Paediatr Drugs* 2017; **19**: 173-181 [PMID: 28434087 DOI: 10.1007/s40272-017-0229-1]
- 67 **Fung SK**, Wong F, Hussain M, Lok AS. Sustained response after a 2-year course of lamivudine treatment of hepatitis B e antigen-negative chronic hepatitis B. *J Viral Hepat* 2004; **11**: 432-438 [PMID: 15357648 DOI: 10.1111/j.1365-2893.2004.00556.x]
  - 68 **Enomoto M**, Tamori A, Kohmoto MT, Hayashi T, Morikawa H, Jomura H, Sakaguchi H, Habu D, Kawada N, Shiomi S, Nishiguchi S. Optimal duration of additional therapy after biochemical and virological responses to lamivudine in patients with HBeAg-negative chronic hepatitis B: a randomized trial. *Hepatol Res* 2008; **38**: 954-959 [PMID: 18498358 DOI: 10.1111/j.1872-034X.2008.00378.x]
  - 69 **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]
  - 70 **Fung J**, Lai CL, Tanaka Y, Mizokami M, Yuen J, Wong DK, Yuen MF. The duration of lamivudine therapy for chronic hepatitis B: cessation vs. continuation of treatment after HBeAg seroconversion. *Am J Gastroenterol* 2009; **104**: 1940-1946; quiz 1947 [PMID: 19455108 DOI: 10.1038/ajg.2009.200]
  - 71 **Wang L**, Liu F, Liu YD, Li XY, Wang JB, Zhang ZH, Wang YZ. Stringent cessation criterion results in better durability of lamivudine treatment: a prospective clinical study in hepatitis B e antigen-positive chronic hepatitis B patients. *J Viral Hepat* 2010; **17**: 298-304 [PMID: 19758278 DOI: 10.1111/j.1365-2893.2009.01178.x]
  - 72 **Kuo YH**, Chen CH, Wang JH, Hung CH, Tseng PL, Lu SN, Changchien CS, Lee CM. Extended lamivudine consolidation therapy in hepatitis B e antigen-positive chronic hepatitis B patients improves sustained hepatitis B e antigen seroconversion. *Scand J Gastroenterol* 2010; **45**: 75-81 [PMID: 20030580 DOI: 10.3109/00365520903394550]
  - 73 **Cai W**, Xie Q, An B, Wang H, Zhou X, Zhao G, Guo Q, Gu R, Bao S. On-treatment serum HBsAg level is predictive of sustained off-treatment virologic response to telbivudine in HBeAg-positive chronic hepatitis B patients. *J Clin Virol* 2010; **48**: 22-26 [PMID: 20233672 DOI: 10.1016/j.jcv.2010.02.014]
  - 74 **Liu F**, Wang L, Li XY, Liu YD, Wang JB, Zhang ZH, Wang YZ. Poor durability of lamivudine effectiveness despite stringent cessation criteria: a prospective clinical study in hepatitis B e antigen-negative chronic hepatitis B patients. *J Gastroenterol Hepatol* 2011; **26**: 456-460 [PMID: 21332542 DOI: 10.1111/j.1440-1746.2010.06492.x]
  - 75 **Jung YK**, Yeon JE, Lee KG, Jung ES, Kim JH, Seo YS, Yim HJ, Um SH, Ryu HS, Byun KS. Virologic response is not durable after adefovir discontinuation in lamivudine-resistant chronic hepatitis B patients. *Korean J Hepatol* 2011; **17**: 261-267 [PMID: 22310790 DOI: 10.3350/kjhep.2011.17.4.261]
  - 76 **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]
  - 77 **Liang Y**, Jiang J, Su M, Liu Z, Guo W, Huang X, Xie R, Ge S, Hu J, Jiang Z, Zhu M, Wong VW, Chan HL. Predictors of relapse in chronic hepatitis B after discontinuation of anti-viral therapy. *Aliment Pharmacol Ther* 2011; **34**: 344-352 [PMID: 21671967 DOI: 10.1111/j.1365-2036.2011.04738.x]
  - 78 **Chang KT**, Ha NB, Trinh HN, Garcia RT, Nguyen HA, Nguyen KK, Garcia G, Ahmed A, Keefe EB, Nguyen MH. High frequency of recurrent viremia after hepatitis B e antigen seroconversion and consolidation therapy. *J Clin Gastroenterol* 2012; **46**: 865-870 [PMID: 22941429 DOI: 10.1097/MCG.0b013e31825ced9]
  - 79 **Ha M**, Zhang G, Diao S, Lin M, Sun L, She H, Kuan C, Shen L, Huang C, Shen W, Huang Z. A prospective clinical study in hepatitis B e antigen-negative chronic hepatitis B patients with stringent cessation criteria for adefovir. *Arch Virol* 2012; **157**: 285-290 [PMID: 22080196 DOI: 10.1007/s00705-011-1163-0]
  - 80 **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]
  - 81 **He D**, Guo S, Chen W, Chen X, Yan G, Wang J, Li M, Zhu P, Huang H, Wang Y. Long-term outcomes after nucleos(t)ide analogues discontinuation in chronic hepatitis B patients with HBeAg-negative. *BMC Infect Dis* 2013; **13**: 458 [PMID: 24090287 DOI: 10.1186/1471-2334-13-458]
  - 82 **Kim YJ**, Kim K, Hwang SH, Kim SS, Lee D, Cheong JY, Cho SW. Durability after discontinuation of nucleos(t)ide therapy in chronic HBeAg negative hepatitis patients. *Clin Mol Hepatol* 2013; **19**: 300-304 [PMID: 24133668 DOI: 10.3350/cmh.2013.19.3.300]
  - 83 **Jeng WJ**, Sheen IS, Chen YC, Hsu CW, Chien RN, Chu CM, Liaw YF. Off-therapy durability of response to entecavir therapy in hepatitis B e antigen-negative chronic hepatitis B patients. *Hepatology* 2013; **58**: 1888-1896 [PMID: 23744454 DOI: 10.1002/hep.26549]
  - 84 **Kwon JH**, Jang JW, Choi JY, Park CH, Yoo SH, Bae SH, Yoon SK. Should lamivudine monotherapy be stopped or continued in patients infected with hepatitis B with favorable responses after more than 5 years of treatment? *J Med Virol* 2013; **85**: 34-42 [PMID: 23154874 DOI: 10.1002/jmv.23421]
  - 85 **Ridrujo E**, Marciano S, Galdame O, Reggiardo MV, Muñoz AE, Adrover R, Cocozzella D, Fernandez N, Estepo C, Mendizábal M, Romero GA, Levi D, Schroder T, Paz S, Fainboim H, Mandó OG, Gadano AC, Silva MO. Relapse rates in chronic hepatitis B naïve patients after discontinuation

- of antiviral therapy with entecavir. *J Viral Hepat* 2014; **21**: 590-596 [PMID: [24188363](#) DOI: [10.1111/jvh.12200](#)]
- 86 **Sohn HR**, Min BY, Song JC, Seong MH, Lee SS, Jang ES, Shin CM, Park YS, Hwang JH, Jeong SH, Kim N, Lee DH, Kim JW. Off-treatment virologic relapse and outcomes of re-treatment in chronic hepatitis B patients who achieved complete viral suppression with oral nucleos(t)ide analogs. *BMC Infect Dis* 2014; **14**: 439 [PMID: [25125320](#) DOI: [10.1186/1471-2334-14-439](#)]
  - 87 **Patwardhan VR**, Sengupta N, Bonder A, Lau D, Afdhal NH. Treatment cessation in noncirrhotic, e-antigen negative chronic hepatitis B is safe and effective following prolonged anti-viral suppression with nucleosides/nucleotides. *Aliment Pharmacol Ther* 2014; **40**: 804-810 [PMID: [25109610](#) DOI: [10.1111/apt.12908](#)]
  - 88 **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](#)]
  - 89 **Jiang JN**, Huang ZL, He LX, Huang YH, Su MH, Xie R, Liang YX, Fu WD, Huang XH, Guo WW, Zhong SH, Liu ZH, Li SH, Zhu TF, Gao ZL. Residual amount of HBV DNA in serum is related to relapse in chronic hepatitis B patients after cessation of nucleos(t)ide analogs. *J Clin Gastroenterol* 2015; **49**: 323-328 [PMID: [25014234](#) DOI: [10.1097/MCG.000000000000170](#)]
  - 90 **Seto WK**, Hui AJ, Wong VW, Wong GL, Liu KS, Lai CL, Yuen MF, Chan HL. Treatment cessation of entecavir in Asian patients with hepatitis B e antigen negative chronic hepatitis B: a multicentre prospective study. *Gut* 2015; **64**: 667-672 [PMID: [24833635](#) DOI: [10.1136/gutjnl-2014-307237](#)]
  - 91 **Peng J**, Cao J, Yu T, Cai S, Li Z, Zhang X, Sun J. Predictors of sustained virologic response after discontinuation of nucleos(t)ide analog treatment for chronic hepatitis B. *Saudi J Gastroenterol* 2015; **21**: 245-253 [PMID: [26228369](#) DOI: [10.4103/1319-3767.161645](#)]
  - 92 **Jeng WJ**, Chen YC, Sheen IS, Lin CL, Hu TH, Chien RN, Liaw YF. Clinical Relapse After Cessation of Tenofovir Therapy in Hepatitis B e Antigen-Negative Patients. *Clin Gastroenterol Hepatol* 2016; **14**: 1813-1820.e1 [PMID: [27404969](#) DOI: [10.1016/j.cgh.2016.07.002](#)]
  - 93 **Qiu YW**, Huang LH, Yang WL, Wang Z, Zhang B, Li YG, Su TT, Zhou HY, Xu W, Wang XD, Dai YP, Gan JH. Hepatitis B surface antigen quantification at hepatitis B e antigen seroconversion predicts virological relapse after the cessation of entecavir treatment in hepatitis B e antigen-positive patients. *Int J Infect Dis* 2016; **43**: 43-48 [PMID: [26523639](#) DOI: [10.1016/j.ijid.2015.10.019](#)]
  - 94 **Yao CC**, Hung CH, Hu TH, Lu SN, Wang JH, Lee CM, Chen CH. Incidence and predictors of HBV relapse after cessation of nucleoside analogues in HBeAg-negative patients with HBsAg  $\leq$  200 IU/mL. *Sci Rep* 2017; **7**: 1839 [PMID: [28500322](#) DOI: [10.1038/s41598-017-02010-w](#)]
  - 95 **Cao J**, Chi H, Yu T, Li Z, Hansen BE, Zhang X, Zhong C, Sun J, Hou J, Janssen HLA, Peng J. Off-Treatment Hepatitis B Virus (HBV) DNA Levels and the Prediction of Relapse After Discontinuation of Nucleos(t)ide Analogue Therapy in Patients With Chronic Hepatitis B: A Prospective Stop Study. *J Infect Dis* 2017; **215**: 581-589 [PMID: [28329347](#) DOI: [10.1093/infdis/jix025](#)]
  - 96 **Chen CH**, Hsu YC, Lu SN, Hung CH, Wang JH, Lee CM, Hu TH. The incidence and predictors of HBV relapse after cessation of tenofovir therapy in chronic hepatitis B patients. *J Viral Hepat* 2018; **25**: 590-597 [PMID: [29274189](#) DOI: [10.1111/jvh.12851](#)]
  - 97 **Hung CH**, Wang JH, Lu SN, Hu TH, Lee CM, Chen CH. Hepatitis B surface antigen loss and clinical outcomes between HBeAg-negative cirrhosis patients who discontinued or continued nucleoside analogue therapy. *J Viral Hepat* 2017; **24**: 599-607 [PMID: [28130815](#) DOI: [10.1111/jvh.12683](#)]
  - 98 **Shinkai N**, Tanaka Y, Orito E, Ito K, Ohno T, Hirashima N, Hasegawa I, Sugauchi F, Ueda R, Mizokami M. Measurement of hepatitis B virus core-related antigen as predicting factor for relapse after cessation of lamivudine therapy for chronic hepatitis B virus infection. *Hepatol Res* 2006; **36**: 272-276 [PMID: [16971173](#) DOI: [10.1016/j.hepres.2006.08.005](#)]
  - 99 **Jung KS**, Park JY, Chon YE, Kim HS, Kang W, Kim BK, Kim SU, Kim do Y, Han KH, Ahn SH. Clinical outcomes and predictors for relapse after cessation of oral antiviral treatment in chronic hepatitis B patients. *J Gastroenterol* 2016; **51**: 830-839 [PMID: [26687058](#) DOI: [10.1007/s00535-015-1153-1](#)]



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