


Clinical management of chronic hepatitis B: A concise overview

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Abstract

Worldwide, over 250 million people are chronically infected with the hepatitis B virus (HBV). Infected patients have an up to 100-fold increased risk for liver-related complications, including cirrhosis, hepatic decompensation and hepatocellular carcinoma. Nonetheless, the majority of the infections remains asymptomatic, stressing the importance of HBV screening and linkage to care. Excellent clinical outcomes are seen during nucleos(t)ide analogue (NA) therapy, which often is continued indefinitely due to a lack of functional cure. Increasing evidence suggests that NA discontinuation following long-term treatment induced viral suppression in patients without a functional cure may be a favourable option. Reliable biomarkers are, however, urgently needed to select the patients that would benefit from NA withdrawal. In addition, renewed and novel approaches to improve screening and linkage to care are other fundamental factors in the optimisation of the clinical management of chronic hepatitis B.

KEYWORDS

chronic hepatitis B, clinical management, nucleos(t)ide analogues, screening, treatment discontinuation

CLINICAL CASE

We here present a case of a 74-year-old male, with chronic hepatitis B (CHB), who developed treatment-refractory liver decompensation and a hepatocellular carcinoma (HCC) several years after nucleos(t)ide analogue (NA) discontinuation.

He was under care in another centre and started on tenofovir disoproxil fumarate (TDF) in 2013 because of a hepatitis B virus (HBV)-related liver cirrhosis complicated by portal hypertension, as evidenced by oesophageal varices and a hepatitis B e antigen (HBeAg)-positive hepatitis. His past medical history also included

diabetes type II, obesity and arterial hypertension. Two years after NA treatment initiation, TDF was discontinued following a NA-induced HBeAg seroconversion and 6 months of consolidation treatment. The patient was lost to follow-up thereafter, but presented another 2 years later at the age of 74 to the emergency department with signs of hepatic encephalopathy. He was subsequently retreated with lamivudine (LAM). Two months later the patient was transferred to our tertiary care hospital with a Child Pugh B decompensated liver cirrhosis, a hepatic encephalopathy stage III and non-bleeding oesophageal varices grade 3, due to a severe HBV relapse with HBeAg seroreversion (HBV DNA 5.73 log IU/mL, alanine

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aminotransferase [ALT] 54 U/L). TDF treatment was restarted immediately and resulted in an initial improvement of liver function and HBV DNA suppression. However, a 4-cm solitary HCC lesion was diagnosed two weeks later, for which a Transarterial Chemoembolization with doxorubicine eluting beads was performed upon review by our multidisciplinary liver tumour board. Unfortunately, the patient developed progressive liver decompensation, characterised by ascites, renal impairment and hepatic encephalopathy. Despite a switch from TDF to tenofovir alafenamide (TAF), the patient's condition deteriorated further and he passed away 6 months later.

Lamentably, at two critical treatment decision points the Belgian reimbursement criteria did, at that time, not allow to manage this case in line with the current European Association for the Study of the Liver (EASL) clinical practice guidelines, which recommend to not discontinue NA treatment in patients with cirrhosis and to retreat with a second-generation NA rather than LAM.

This case further highlights the importance of universal NA treatment stop criteria and stresses the need for close follow-up after NA treatment cessation in order to detect a relapse and CHB complications early on.

INTRODUCTION

With approximately 3.6% of the global population infected, HBV infections remain a serious global health problem. Hepatitis B is most endemic in Asia and sub-Saharan Africa, with seroprevalence rates of >8%, whereas seroprevalence rates in Europe vary between <1% in Western Europe and <5% in Eastern Europe. The lowest HBV seroprevalence rates are reported in the United States (0.7%).¹

Chronically infected patients remain hepatitis B surface antigen (HBsAg) seropositive for >6 months and show an up to 100-fold increased risk for liver-related complications, including cirrhosis, hepatic decompensation and HCC, ultimately resulting in liver-related death. As such, the virus continues to kill over 700,000 people annually. Importantly, the number of HBV-induced end-stage liver diseases and liver cancers is on the rise, ranking HBV as one of the most common causes of death worldwide.¹

If managed appropriately, many CHB related deaths can be prevented with survival rates mirroring these of the general population.² In this review, we will give a concise overview of key aspects of the background and clinical management of CHB, with a focus on new insight in NA treatment.

TESTING, SCREENING AND LINKAGE TO CARE

Since chronic infections with HBV remain mostly asymptomatic, screening for HBV and linking HBsAg positive patients to care is of crucial importance. Low linkage to care rates of approximately 30% in non-hospital-based screening programs, especially for ethnic minorities with high HBsAg seroprevalence rates, call for innovative

approaches to reach the World Health Organisation's (WHO) target of eliminating viral hepatitis by 2030.³ Different HBV screening strategies, using venepuncture or fingerstick point of care testing (POCT) in either community- or hospital-based settings have been described. In our own study, we have shown that in an Asian migrant population with an HBsAg prevalence of 6.8%, opportunistic testing using finger stick POCT increased linkage to care from 34% to 86%, which coincided with an on the spot-diagnosis and immediate referral to specialist care.⁴ This approach might therefore be more appropriate in reaching ethnic minorities in low HBsAg seroprevalence regions, such as Europe.

NATURAL HISTORY OF CHRONIC HEPATITIS B

An overview of the natural history of CHB is depicted in Figure 1. The EASL has introduced a new nomenclature to describe the natural history of CHB in their latest management guidelines.⁵ These differ from previous nomenclature by departing from concepts such as 'asymptomatic carrier', which may introduce reduced monitoring and increase risk to losing track of patients. This comes on top of the known complexity of the other stages of the natural history of HBV infection, and the different actions physicians need to take for follow-up and management. In its core, the EASL nomenclature reflects the contrast between chronic infection by HBV—which implies no treatment but close monitoring of HBsAg, HBeAg, hepatitis B e antibodies (anti-HBe), HBV DNA, ALT and liver fibrosis. On the contrary, there is chronic hepatitis, which is a treatment indication if there is proof of significant viral replication. The immunological processes that govern these phases and its transition are still being unravelled, despite intense research efforts.^{1,6-8}

TREATMENT INDICATIONS AND OUTPATIENT FOLLOW-UP

Treatment should be considered in clinical settings with significant viral replication, liver damage and/or fibrosis and should be based on viral load, ALT levels, liver elastography and/or histology (Figure 1). As fibrosis stage is generally considered to be the most important prognostic factor, special attention should be given to patients with at least moderate (F2) liver fibrosis.

When evaluating the need for treatment, the patient's age and health status, the risk of HBV transmission, cirrhosis, family history of HCC or cirrhosis, previous treatment history and extrahepatic manifestations should be taken into account. Different recommendations are applicable for pregnant patients, coinfecting patients and/or patients that are under chemo- or immunosuppressive therapy.⁵

Patients that do not fulfil the treatment indications should be monitored on a 3- to 6-monthly basis with serum HBV DNA, ALT, HBsAg, HBeAg, anti-HBe and fibrosis assessments (Figure 1). This should be complemented with liver ultrasonography for HCC

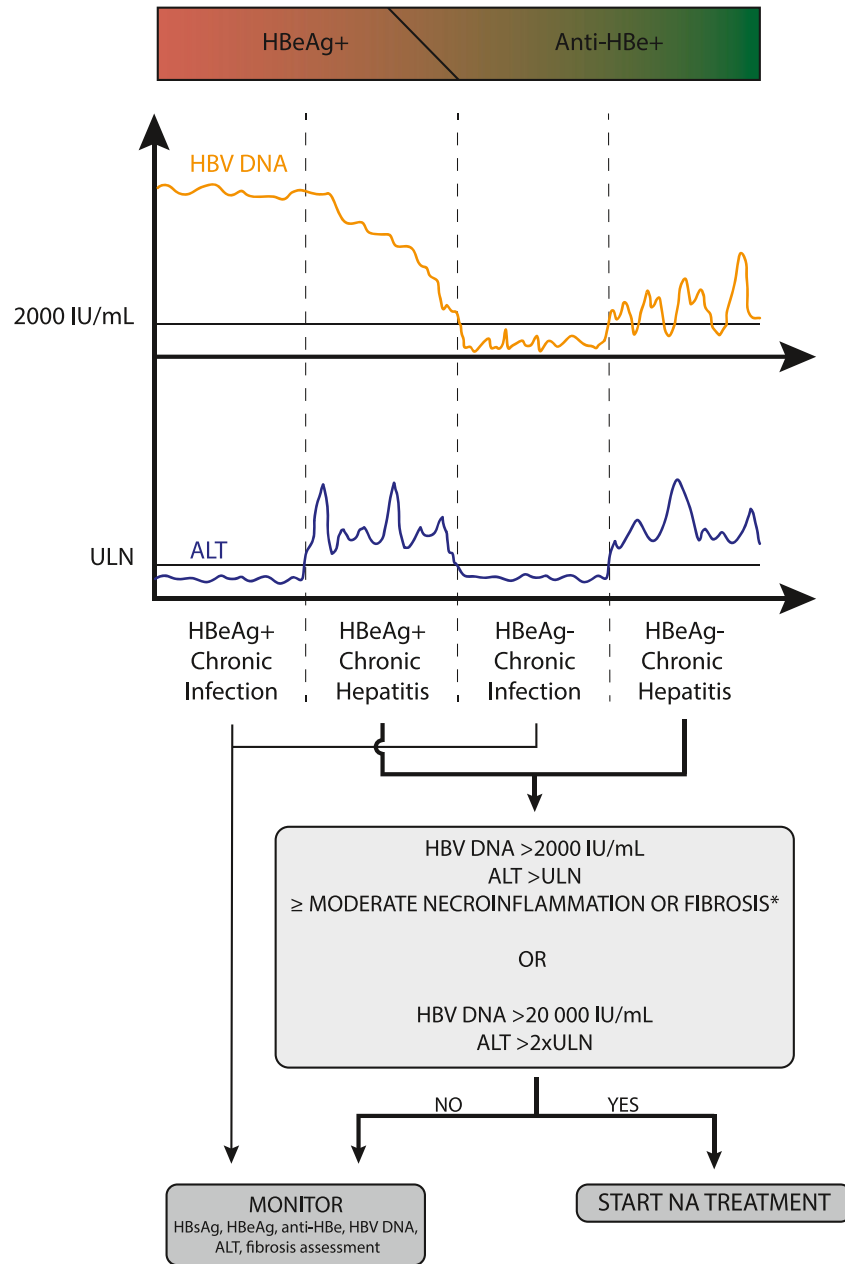


FIGURE 1 Schematic overview of the natural history and treatment indications of chronic hepatitis B. *Determined in a liver biopsy or using a validated non-invasive method. ALT, alanine aminotransferase; Anti-HBe, hepatitis B e antibodies; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, nucleos(t)ide analogue(s); ULN, upper limit of normal

surveillance according to age and ethnicity categories, when the annual HCC incidence risk exceeds 0.2%.^{5,9}

TREATMENT OPTIONS

To this day, there is no definitive cure for CHB, considering that current treatment options are not able to eliminate HBV DNA integrated into the host genome, and only rarely in the long-term eradicate the HBV's covalently closed circular DNA (cccDNA), a minichromosome that resides in the nucleus of all infected cells.

HBsAg loss is considered the ultimate goal in the management of CHB, as it confers excellent clinical outcomes.¹⁰ Therefore, patients with a confirmed HBsAg loss and absence of advanced liver fibrosis can be discharged from active follow-up and are considered functionally cured.⁵

Until the introduction of LAM in the nineties, (pegylated) interferon (IFN) was the only available treatment. It induces a long-term immunological response, as evidenced by moderate virologic response and HBeAg seroconversion rates of up to 63% and 27% respectively, and has a finite treatment duration with a <5% chance of functional cure after 48 weeks of treatment (Table 1). However, IFN

TABLE 1 Results of the registration studies for the currently recommended treatment options for chronic hepatitis B after 48 weeks of treatment

	PegIFN- α 2a ¹¹		ETV ¹¹		TDF ¹¹		TAF ^{12,13}	
	HBeAg+	HBeAg–	HBeAg+	HBeAg–	HBeAg+	HBeAg–	HBeAg+	HBeAg–
Number of patients (n =)	271	177	354	325	176	250	581	285
Virologic response ^a (% of patients with HBV DNA < X copies/mL)	25	63	67	90	76	93	64	94
ALT < ULN (%)	39	38	68	78	68	76	72	83
HBsAg loss (%)	±3	±4	2	0	3.2	0	1	0
HBeAg seroconversion (%)	27	/	21	/	21	/	10	/

Abbreviations: ALT, alanine aminotransferase; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PegIFN- α 2a, pegylated interferon α 2a; RCT, randomised controlled trial; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

^aVirological response as defined according to RCT: serum HBV DNA <400 copies/mL (PegIFN- α 2a), <300 copies/mL (ETV), <69 IU/mL (=400 copies/mL) (TDF); <29 IU/mL (TAF).

treatment comes with high variabilities in response, an unfavourable side effect profile and a need for subcutaneous administration.⁵ This side effect profile also prohibits the use of IFN in patients with decompensated cirrhosis, autoimmune disease, psychosis and uncontrolled severe depression, and in female patients during pregnancy and/or lactation.¹¹

Since their introduction, NAs have rapidly become the golden standard for treating CHB. They efficiently suppress viral replication through inhibition of the viral DNA polymerase, stop hepatic necroinflammation and fibrogenesis and substantially reduce the risk of HCC development, resulting in overall survival rates that are similar to the general population.² First generation NAs, including LAM and adefovir, come with a low barrier for resistance. Since resistance is almost absent (<1% after 5 years of treatment) with second-generation NAs, consisting of entecavir (ETV), TDF and TAF, the use of first-generation NAs has largely been abandoned.

All second-generation NAs have similar efficacies (Table 1) and a favourable safety profile. However, in a head-to-head non-inferiority randomised controlled trial (RCT) of TAF versus TDF, a higher decrease in estimated glomerular filtration (eGFR) rate of 4–5 ml/min versus 1–2 ml/min and bone mineral density (BMD) of 1.7%–2.5% versus 0.1%–0.9% at 1 year of treatment was observed in the TDF versus the TAF treated group, respectively.^{5,12,13} In a follow-up non-inferiority RCT, TDF-treated patients continued their treatment or switched to TAF, which resulted in improvements in BMD (+0.7%–1.7%) and eGFR (+0.9 ml/min) at 48 weeks for the TAF-switched patients.¹⁴ Given the non-inferiority study designs, it is difficult to establish superiority of TAF over TDF for the observed small differences in eGFR and BMD. In addition, the clinical relevance of these changes is currently not clear, as reported long-term clinical outcomes in real-world studies and TDF registration trials have been excellent.¹⁵ Furthermore, cases of TDF-associated nephrotoxicity have mostly been described in the TDF-treated HIV-infected population on combination antiretroviral treatment.

Similarly, superiority of TAF versus ETV in patients at risk for nephrotoxicity is yet to be established, as no head-to-head studies comparing both drugs are available. TAF has, however, been studied in hard-to-treat end-stage-renal disease patients, such as patients on intermittent haemodialysis, which makes it an evident first choice in this setting. Nonetheless, TAF is only approved by the European Medicines Agency and Food and Drug Administration since 2017 and 2016, respectively. Therefore, long-term efficacy and safety data are lacking.^{12,13,16}

Patients under NA treatment should be monitored lifelong until HBsAg seroclearance, using at least serum HBV DNA and ALT testing every 3 to 4 months during the first year after treatment start and every 6 months thereafter. HBsAg should be checked every 12 months in patients with undetectable serum HBV DNA levels. Patients with a medium to high risk of HCC development may require additional HCC surveillance using liver ultrasonography.⁵

Unfortunately, despite efficient suppression of HBV DNA, HBsAg loss is rare during NA treatment, as only 0.15% of the patients on long-term NA therapy clear HBsAg annually. Lifelong treatment here is often indicated. The latter comes with a risk for still unknown long-term side effects and non-adherence.⁵

NUCLEOS(T)IDE ANALOGUE TREATMENT CESSATION

Since HBsAg loss is rare during NA treatment, many efforts have been made to identify optimal stopping criteria prior to HBsAg loss. From a scientific point of view, treatment withdrawal may induce a rebound of viral replication and viral protein production, leading to a rechallenging of the immune system with induction of vigorous T cell responses, potentially necessary for a functional cure.

TABLE 2 Summary of all major prospective nucleos(t)ide analogue stop studies with at least 72 weeks of off-treatment follow-up

Author, year and design	Asians/Caucasian/other (%)	Number of patients (n =)		On NA viral suppression (years)		Off-treatment follow-up (years)	HBsAg loss (%)		Sustained response (%)		Clinical relapse (%)		Retreatment (%)		Decompensation, HCC or death (n =)
		+	-	+	-		+	-	+	-	+	-	+	-	
		HBsAg	HBeAg	HBsAg	HBeAg		HBsAg	HBeAg	HBsAg	HBeAg	HBsAg	HBeAg	HBsAg	HBeAg	
Berg et al. 2017 ¹⁹	4.8/88.1/7.2	-	21	-	>3.5	3.0	-	19	-	24	-	-	-	38	0
Liem et al. 2019 ²⁰	98/2/0	18	27	3.4	7.1	1.5	0	4	17	33	6	19	61	22	0
Bömmel et al. 2020 ²¹	-/78.5/-	-	79	-	-	1.8	-	10.3	-	40.5 ^a	-	45.6 ^b	-	13.9	0
Cao et al. 2017 ²²	100/0/0	60	22	2.1	2.9	2.0	6.1	6.1	29	29	31	53	31	53	0
Chi et al. 2019 ²³	100/0/0	71	29	2.2	2.9	2.6	4	10	-	-	43	59	43	59	0
Liu et al. 2018 ²⁴	100/0/0	138	85	1.5	2.5	10.0	8	14	-	-	-	-	28	28	1 (HCC)
Papatheodoridis et al. 2018 ³⁰	0/100/0	-	57	-	5.3	1.5	-	25	-	86	-	33	-	28	0
Su et al. 2018 ²⁵	100	28	72	2.2	2.2	>2.6	0	0	-	-	-	-	40	40	0
Wong et al. 2018 ²⁶	100	-	20	-	-	4.0	-	0	-	0	-	50	-	55	0
Garcia-Lopez et al. 2021 ²⁷	-/93/-	-	27	-	8.0	2.0	-	30	-	48	-	19	-	19	0
TOTAL		315	439	1.5-3.4	2.5-8.0	1.5-10.0	0-8	0-30	17-29	0-86	6-43	19-59	28-61	13.9-59	0-1

Note: Clinical relapse, HBV DNA > 2000 IU/mL and ALT > 2xULN; Sustained response, HBV DNA < 2000 IU/mL ≥6 months; The sum of the percentages may be >100% due to rounding. Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; NA, nucleos(t)ide analogue(s); ULN, upper limit of normal. ^aPercentage of patients with HBV DNA < 2000 IU/ml and ALT < ULN. ^bPercentage of patients with HBV DNA > 2000 IU/ml and ALT > ULN.

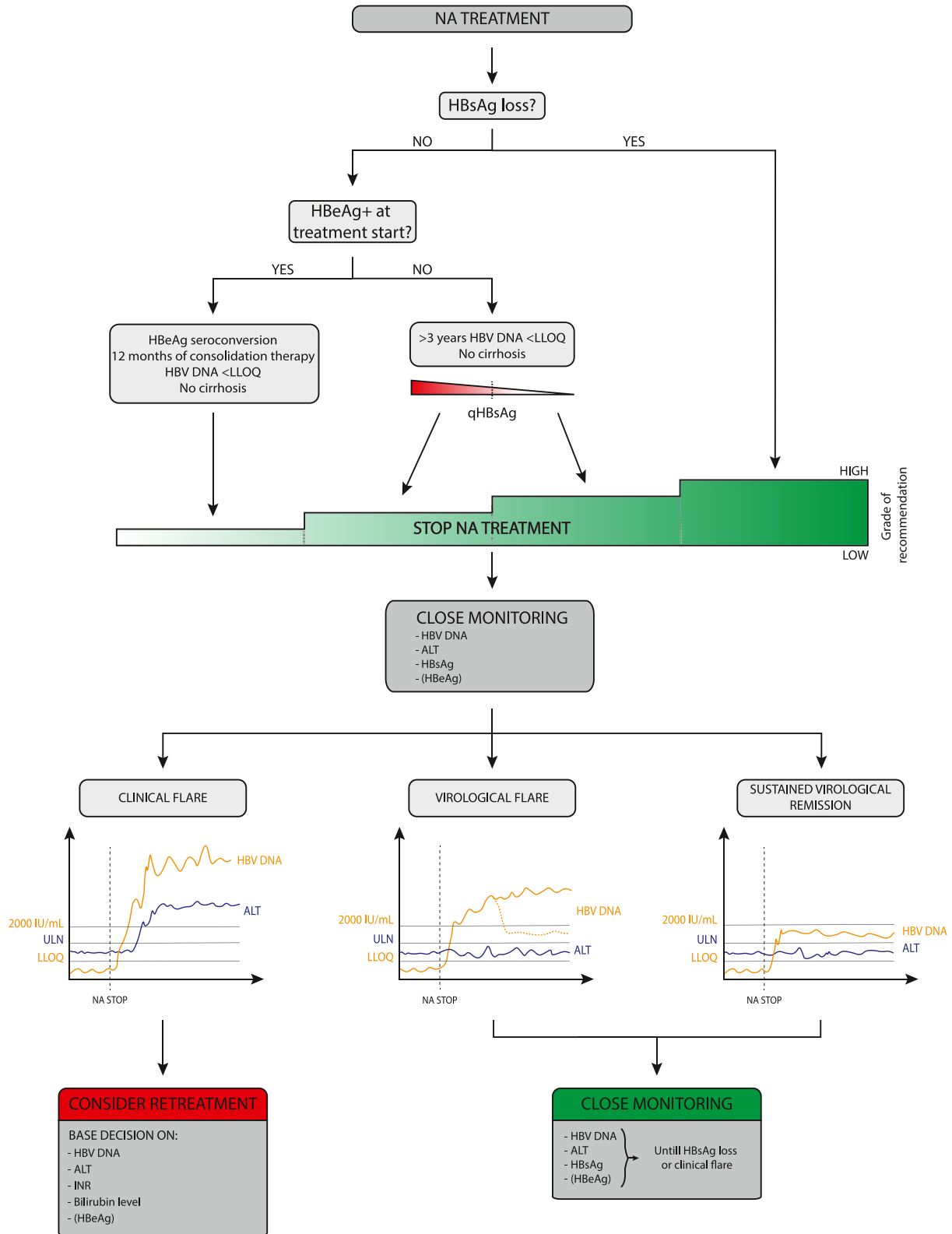


FIGURE 2 Overview of the indications for treatment discontinuation and typical scenarios observed after treatment discontinuation. NA: nucleos(t)ide analogue(s). ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; INR, international normalised ratio; LLOQ, lower limit of quantification; qHBsAg, quantitative hepatitis B surface antigen; ULN, upper limit of normal

All major international guidelines (American, European and Asian) suggest discontinuing treatment in non-cirrhotic patients who show a HBeAg seroconversion under NA treatment, provided a period of 1–3 years of consolidation therapy with undetectable HBV DNA levels is completed. The stopping rules for start of treatment HBeAg negative patients are a little more contradictory. The European and Asian guidelines state that these patients could stop NA treatment in the absence of signs of cirrhosis after at least 2–3 years of NA-induced virological suppression, whilst in contrast, the American guidelines only recommend NA treatment cessation after confirmed HBsAg loss.^{5,9,17}

So far, the scientific evidence behind these recommendations is rather limited and a great deal of the studies that have been performed show contradictory results. In addition, the observed results strongly depend on the included population, defined primary outcome, relapse definitions, monitoring frequencies, retreatment criteria and follow-up time, complicating interstudy comparison. A meta-analysis including 1716 patients from 25 individual studies reported a pooled durable virologic remission rate of 38% at 3 years after NA treatment cessation, being higher in start of treatment HBeAg positive (51.5%) than in HBeAg negative patients (30.1%).¹⁸ These results thus suggest that one third to half of the patients who stop NA treatment could remain off-treatment for at least three years. Similar response rates were observed in more recent prospective studies, as can be seen in Table 2.

Although there is a good chance of sustained virological remission (HBV DNA < 2000 IU/ml and ALT < 2x upper limit of normal [ULN]) after treatment cessation, the risk of relapse with subsequent flares remains substantial. Close follow-up is therefore mandatory until HBsAg loss is achieved or retreatment is indicated (Figure 2). Although the optimal off-treatment follow-up interval is not yet established, a follow-up consult every 2 to 4 weeks the first 3 months and every 6 weeks thereafter until month 6, is envisaged to be required since most flares were observed within this timeframe in the prospective NA-stop studies.^{18–27} If diagnosed in time, severe flares can be managed by reinitiating treatment. So far, apart from our above mentioned case, 11 liver-related deaths have been reported after NA treatment cessation. All were reported in retrospective studies where follow-up was at the discretion of the treating physician.²⁸

Recently, in the prospective NA stop Toronto trial, start of treatment HBeAg positive patients were three times more likely to require retreatment for relapse than start of treatment HBeAg negative patients (61% vs. 22%, respectively).²⁰ Other prospective studies confirm such high relapse rates in start of treatment HBeAg positive patients, together with low HBsAg loss rates (Table 2). According to our own experience and the abovementioned studies, which contrasts with most international guidelines, the benefit of NA withdrawal in pre-treatment HBeAg positive patients may be limited and we therefore would not propose to stop NA in these patients (Figure 2).²⁹

As can be observed in Table 2, data from NA cessation in patients who were HBeAg negative at treatment start are more conflicting. Although these studies report relatively high relapse rates, a good proportion of the participants seem to develop sustained virological remission. Moreover, up to 30% of the participating pre-treatment HBeAg negative patients appear to attain a functional cure at end of follow-up.

Unfortunately, no validated biomarkers to predict a patient's response after treatment cessation are available. Increasing evidence suggests that HBsAg kinetics play an important role in the outcome of the patients after treatment withdrawal. As such, start of treatment HBeAg negative patients with a low HBsAg level (<100 IU/ml) at the end of treatment tend to have a better chance of off-treatment HBsAg loss and sustained virological remission, resulting in a higher grade of recommendation to discontinue NA treatment in such patients (Figure 2).³¹ Several other viral biomarkers, including HBV pregenomic RNA and HBV core related antigen are currently under investigation. However, there are no or limited commercial assays available that can be used in clinical practice.³²

Another interesting finding from the major prospective studies on NA treatment cessation is that studies with predominantly Caucasian patients appear to observe lower relapse rates and higher HBsAg seroclearance rates (Table 2). These findings are corroborated by retrospective data from our group where Caucasian patients had about a 6-fold higher annual HBsAg loss rate compared to non-Caucasian patients.³³

In conclusion, with the introduction of potent NAs, CHB has become a well manageable disease with excellent clinical outcomes. Unfortunately, long-term treatment is often indicated because NA-induced HBsAg loss only occurs rarely. Remarkably, higher HBsAg loss rates are seen after NA treatment withdrawal. Therefore, there is an urgent need to define the subpopulation that benefits most from treatment cessation. Moreover, novel treatments and future approaches should focus on elimination of the HBV cccDNA from infected cells and increasing functional cure rates.³⁴ In addition, renewed and novel approaches to improve screening and linkage to care are other fundamental factors in the aim to reach the WHO goal of hepatitis B elimination by 2030.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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