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When to start or stop therapy in CHB - 2025 update

Pietro Lampertico, MD, PhD

Gastroenterology and Hepatology Division
Fondazione IRCCS Cà Granda - Ospedale Maggiore Policlinico
University of Milan - Italy

Disclosures

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-

**What can I say to George and other friends
on this topic ?**

What's is really new ?

EASL 2025 Clinical Practice Guidelines on HBV management

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Clinical Practice Guidelines

JOURNAL
OF HEPATOLOGY

EASL Clinical Practice Guidelines on the management of hepatitis B virus infection^{*}

⁰¹⁸ European Association for the Study of the Liver^{*}

Summary

The updated EASL Clinical Practice Guidelines on the management of hepatitis B virus (HBV) infection provide comprehensive, evidence-based recommendations for its management. Spanning ten thematic sections, the guidelines address diagnostics, treatment goals, treatment indications, therapeutic options, hepatocellular carcinoma surveillance, management of special populations, HBV reactivation prophylaxis, post-transplant care, HBV prevention strategies, and finally address open questions and future research directions. Chronic HBV remains a global health challenge, with over 250 million individuals affected and significant mortality due to cirrhosis and hepatocellular carcinoma. These guidelines emphasise the importance of early diagnosis, risk stratification based on viral and host factors, and tailored antiviral therapy. Attention is given to simplified algorithms, vaccination, and screening to support global HBV elimination targets. The guidelines also discuss emerging biomarkers and evolving definitions of functional and partial cure. Developed through literature review, expert consensus, and a Delphi process, the guidelines aim to equip healthcare providers across disciplines with practical tools to optimise HBV care and outcomes worldwide.

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Introduction

Hepatitis B virus (HBV) infection continues to be a significant global health challenge, affecting millions of individuals worldwide. Chronic HBV infection can lead to severe liver diseases, including cirrhosis and hepatocellular carcinoma (HCC), causing substantial morbidity and mortality. As the medical community strives to improve the management of this complex and evolving disease, there is a critical need for comprehensive and up-to-date guidance that addresses the diagnosis, treatment and prevention of HBV infection.

The European Association for the Study of the Liver (EASL) clinical practice guidelines (CPGs) on HBV have been developed to serve as a practical resource for physicians, encompassing both general practitioners and specialists, who play a pivotal role in the care of individuals with HBV infection. With its

infection. It emphasises the importance of screening, regular follow-up, early intervention, and personalised care to enhance patient outcomes. Furthermore, this guideline addresses a pressing issue that pertains to resource-limited regions, such as many parts of Africa and Asia. Recognising the challenges

Methodology and implementation

The development of this guideline was guided by a rigorous

Introduction

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The European Association for the Study of the Liver (EASL) clinical practice guidelines (CPGs) on HBV have been developed to serve as a practical resource for physicians, encompassing both general practitioners and specialists, who play a pivotal role in the care of individuals with HBV infection. With its evidence-based recommendations and expert insights, the aim of this guideline is to empower healthcare professionals with the knowledge and tools necessary to make informed clinical decisions tailored to the unique needs of each patient.

The guideline covers a wide spectrum of topics, ranging from diagnostics, patient evaluation and treatment indications to antiviral therapy options, monitoring strategies, HCC surveillance, considerations for special populations, prophylaxis of HBV reactivation (HBVr), and finally the prevention of HBV

infection. It emphasises the importance of screening, regular follow-up, early intervention, and personalised care to enhance patient outcomes. Furthermore, this guideline addresses a pressing issue that pertains to resource-limited regions, such as many parts of Africa and Asia. Recognising the challenges faced in these areas, where healthcare resources may be scarce, the guideline explores strategies for simplifying HBV management while maintaining efficacy. By acknowledging the diverse healthcare landscapes around the world, this guideline aims to contribute to the improved management of HBV infection on a global scale.

Methodology and implementation

The development of this guideline was guided by a rigorous and systematic approach based on EASL standard operating policies.¹ The methodology employed a comprehensive and evidence-based process to ensure the validity, reliability, and applicability of the recommendations provided within this guideline.

Expert panel formation

An expert panel consisting of hepatologists and infectious disease specialists was selected by the EASL Governing Board.

^{*} Corresponding author. Address: European Association for the Study of the Liver, The EASL Building – Home of Hepatology, 7 rue Daubin, CH 1203 Geneva, Switzerland. Tel: +41 (0) 22 807 03 60. E-mail address: easloffice@easloffice.eu

¹ Clinical Practice Guideline Panel: Chair: Markus Comberg; Secretary to the Chair: Lisa Sandmann; Panel members: Jerzy Jaroszewicz, Patrick Kennedy, Pietro Lampertico, Maud Lemoine, Sabela Lens, Barbara Testoni, Grace Lai-Hung Wong; EASL Governing Board representative: Francesco Paolo Russo.

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Under embargo until EASL 2025!!

To be published in J Hepatol 2025 soon...

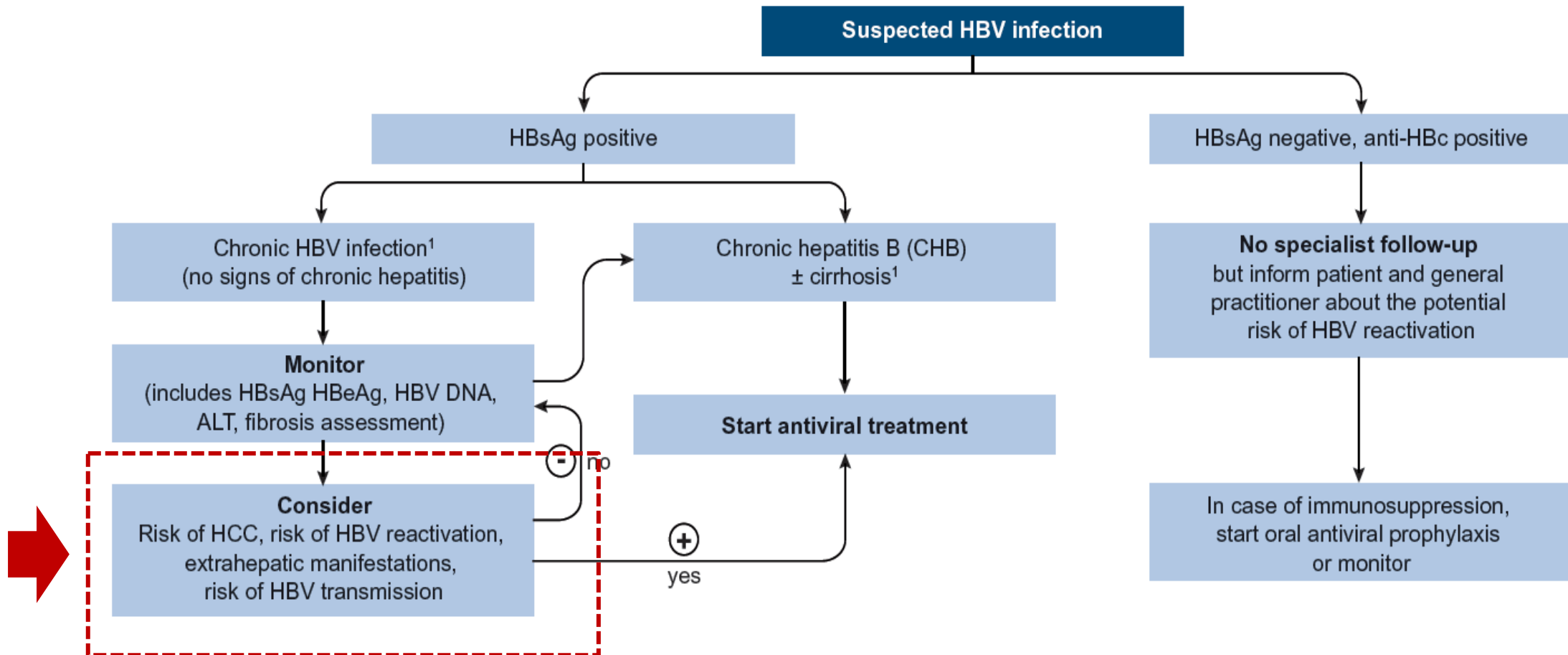
To be presented at EASL 2025 on Saturday May 10th, 9:45 AM

When to start therapy (NUC)

EASL 2017 Guidelines - indications for HBV treatment

PHASE	1	2	3	4
New terminology	HBeAg positive Chronic <i>infection</i>	HBeAg positive Chronic <i>hepatitis</i>	HBeAg negative Chronic <i>infection</i>	HBeAg negative Chronic <i>hepatitis</i>
Old terminology	<i>Immune tolerant</i>	<i>HBeAg-positive CHB</i>	<i>Inactive carrier</i>	<i>HBeAg-negative CHB</i>
HBsAg	High	High/Intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10 ⁷ IU/mL	10 ⁴ –10 ⁷ IU/mL	<2,000 IU/mL*	>2,000 IU/mL
ALT	Normal	Elevated	Normal	Elevated**
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Disease progression	Low	Moderate to high	None	Moderate to high
Treatment	Not indicated***	Indicated	Not indicated	Indicated

EASL 2017 Guidelines - Algorithm for the management of HBV



NB most of my CHB patients in phase 1, 2 and 4 are on long-term NUC therapy !

EASL 2025 Guidelines - Natural history and Clinical phases of HBV

Table 4. Phase of chronic HBV infection, modified based on.⁵

	Phase 1	Phase 2	Phase 3	Phase 4
	HBeAg-positive chronic infection	HBeAg-positive chronic hepatitis	HBeAg-negative chronic infection	HBeAg-negative chronic hepatitis
HBsAg	High	Intermediate to high	Low, usually <1,000 IU/ml	Intermediate, usually >1,000 IU/ml
HBV DNA	High, usually $\geq 10^7$ IU/ml	Moderate to high, usually 10^4 - 10^7 IU/ml	Usually <2,000 IU/ml	Usually, >2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease progression (if untreated)	None/minimal	Moderate to severe	None	Mild to severe

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

*Either persistently or intermittently.

857,000) and cases of decompensated cirrhosis (from 296,000 to 403,000), assuming that current levels of diagnosis and treatment remain unchanged.⁴

Understanding the natural history of HBV infection is crucial for identifying individuals at risk of disease progression. The transition from acute to chronic infection and the potential for reactivation necessitate comprehensive surveillance and timely intervention. Chronic HBV infection is a dynamic and complex condition that progresses through distinct phases (Table 4), each characterised by unique virological, immunological and clinical features. A comprehensive understanding of these phases is essential for accurate diagnosis, tailored management, and informed decision-making in patient care.

A significant proportion of individuals with chronic HBV infection cannot be easily classified into the four phases outlined in the 2017 EASL CPGs,⁵ which are also adopted in this new guideline. For example, numerous publications have

classified patients as being in a "grey zone" or "intermediate phase",⁶⁻⁸ highlighting the large heterogeneity within chronic HBV infection. For clarity, it is recommended to avoid these terms and to define the treatment indication based on the current phases (Section 3 of this guideline), while a simplified treatment algorithm independent of hepatitis B e antigen (HBeAg) status is proposed (Fig. 1). That said, a differentiated nomenclature is suggested for research purposes, which is described in detail in Table S1. While categorising patients into "disease phases" is pertinent for research purposes, patient stratification for clinical trials, and indications for antiviral therapy, this complexity can pose challenges in clinical practice. Therefore, the recommendations in this guideline aim to simplify these categorisations, providing healthcare professionals with clear guidance for the effective management of chronic HBV infection to ensure optimal care and improved patient outcomes (Fig. 2).

No «grey zone» or «intermediate phase» patients !

EASL 2025 Guidelines – HBV phases for research purposes

	Population	HBeAg	ALT	HBV DNA	HBsAg	Specifics	Serum HBcrAg	Serum HBV RNA
Phase 1	HBeAg-positive infection, high replicative		Normal (low normal)	Very high, usually $\geq 10^8$	Very high, $\geq 25,000$ IU/ml	Young age, no/mild fibrosis, no disease progression if stable	Positive ++++	Positive ++++
	HBeAg-positive infection, impending phase transition	Positive	Normal (high normal)	High, usually $\geq 10^6$	High but $< 25,000$ IU/mL (or between 20,000-1,000,000 IU/mL)	Age usually ≥ 30 years, fibrosis can be present	Positive ++++	Positive ++++
Phase 2	HBeAg-positive hepatitis		Elevated	High, usually $\geq 10^4$	Moderate to high but $< 25,000$ IU/mL (or $< 20,000$ IU/mL)	Any age, high risk for disease progression	Positive ++++	Positive ++++
	HBeAg-positive cACLD		Normal or elevated	Usually high, but any HBV DNA is possible	Usually high, but any HBsAg is possible	Significant fibrosis, cirrhosis (cACLD is defined as LSM > 10 kPa)	Positive ++++	Positive Any value is possible
	HBeAg-negative cACLD		Normal or elevated	Usually high, but any HBV DNA is possible	Usually high, but any HBsAg is possible	Significant fibrosis, cirrhosis (cACLD is defined as LSM > 10 kPa)	Positive +++	Positive Any value is possible
Phase 3	HBeAg-negative hepatitis		Elevated	Usually $\geq 2,000$ IU/mL	Low to high	high risk for disease progression	Positive ++	Positive or negative Any value is possible
	HBeAg-negative infection, high replicative, high risk infection	Negative	Normal	Usually $> 20,000$ IU/mL	Low to high	Usually older age, fibrosis	Positive ++	Positive Any value is possible
	HBeAg-negative infection, high replicative, low risk infection		Normal	Usually $> 2,000$ IU/mL - 20,000 IU/mL	Low to high	no disease progression if stable for ≥ 3 years	Positive ++	Positive or negative Any value is possible
Phase 4	HBeAg-negative infection, low replicative		Normal (low normal)	$< 2,000$ IU/mL	Usually $< 1,000$ IU/mL	No/mild fibrosis, no disease progression if stable	Negative or +	Negative or +
	HBeAg-negative infection, partial functional cure		Normal (low normal)	Not detectable	< 100 IU/mL	high chance to achieve HBsAg loss	Negative or +	negative
	HBsAg-negative (functional cure)		Normal	Not detectable	< 0.05 IU/mL	Associated with best prognosis	Negative or +	Negative

cACLD: compensated advanced chronic liver disease

Table S1

treatment algorithm independent of hepatitis B e antigen (HBeAg) status is proposed (Fig. 1). That said, a differentiated nomenclature is suggested for research purposes, which is described in detail in Table S1. While categorising patients into “disease phases” is pertinent for research purposes, patient stratification for clinical trials, and indications for antiviral therapy, this complexity can pose challenges in clinical practice. Therefore, the recommendations in this guideline aim to simplify these categorisations, providing healthcare professionals with clear guidance for the effective management of chronic HBV infection to ensure optimal care and improved patient outcomes (Fig. 2).

9 HBsAg positive phases and 2 HBsAg negative phases (and No Occult Infection)

EASL 2025 guidelines -Treatment indication for chronic HBV infection

Treatment indications

Which patients with chronic HBV infection should be treated?

Statements

- In principle, all HBsAg-positive individuals with detectable HBV DNA are candidates for antiviral therapy. The indication for treatment is primarily based on HBV DNA and ALT levels, fibrosis stage and risk of liver disease progression and HCC (**strong consensus**).

Recommendation

- Patients with HBeAg-positive or HBeAg-negative chronic hepatitis B, HBV DNA level $\geq 2,000$ IU/ml and elevated ALT ($>ULN$) and/or significant fibrosis should receive antiviral therapy (**LoE 1, strong recommendation, strong consensus**).
- Patients with cirrhosis should be treated if HBV DNA is detectable, regardless of the level of viraemia and serum ALT (**LoE 3, strong recommendation, strong consensus**).
- Patients with advanced liver disease (corresponding to Metavir fibrosis score $\geq F3$ on liver histology or defined by a LSM ≥ 8 kPa) can be treated if HBV DNA is detectable, regardless of the level of viraemia and serum ALT (**LoE 5, weak recommendation, strong consensus**).
- Patients with persistently low HBV DNA ($<2,000$ IU/ml) and persistently elevated ALT ($>ULN$) can be treated. However, it should be considered that other liver diseases may also be implicated (**LoE 5, weak recommendation, consensus**).

Statement

- Individuals with HBeAg-positive or HBeAg-negative chronic HBV infection require a personalised assessment to determine the appropriate treatment indication (see sections 3.2 and 3.3) (**strong consensus**).

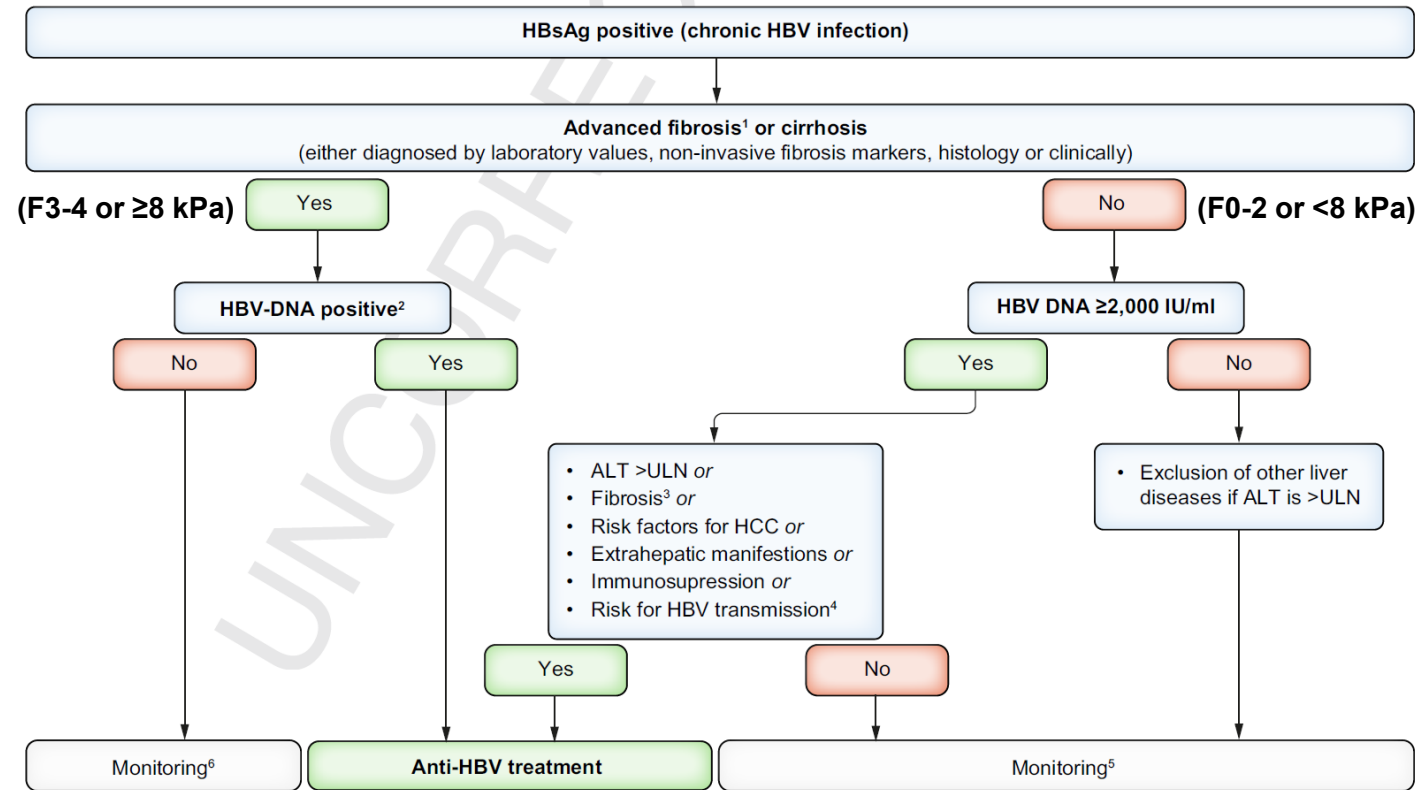


Fig. 1. Treatment indication for chronic HBV infection. ¹Equivalent of ISHAK F ≥ 4 /Metavir F ≥ 3 (non-invasive assessment is preferred, LSM ≥ 8 kPa). ²Sensitive NAT assay (lower limit of detection <20 U/L). ³Equivalent of ISHAK $\geq F3$ /Metavir $\geq F2$ (non-invasive assessment is preferred, LSM ≥ 7 kPa). ⁴The threshold values for HBV DNA vary depending on the activity and risk of transmission. Important: Tenofovir in pregnant women with HBV DNA $\geq 200,000$ IU/ml. ⁵Anti-HBV treatment in HCC, HIV co-infection, extrahepatic manifestations, immunosuppression. ⁶Anti-HBV treatment in immunosuppression. ALT, alanine aminotransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; LSM liver stiffness measurement; ULN, upper limit of normal.

EASL 2025 guidelines-Treatment indication for chronic HBV

Should patients with HBeAg-positive chronic HBV infection be treated?

Statement

- In young individuals (<30 years) with HBeAg-positive chronic HBV infection, persistently normal ALT levels, no significant liver fibrosis, no family history of HCC and no immunosuppressive condition, current clinical evidence does not support immediate antiviral treatment. However, the potential benefits of early therapy – such as reducing HBV DNA integration and clonal expansion – should be balanced against the need for strict adherence to long-term daily treatment and the difficulty of achieving rapid and complete viral suppression in patients with high viral loads (**strong consensus**).

Recommendations

- Individuals with HbeAg-positive chronic infection and an increased HCC risk should be treated (**LoE 3, strong recommendation, strong consensus**).
- Individuals with HbeAg-positive chronic infection and HBV-related extrahepatic manifestations should be treated (**LoE 4, strong recommendation, strong consensus**).
- Individuals with HbeAg-positive chronic infection who are being considered for immunosuppressive therapy or who are immunocompromised should receive antiviral treatment (specific recommendation see 7.1) to prevent hepatitis (**LoE 2, strong recommendation, strong consensus**).
- Selected individuals with HbeAg-positive chronic infection can be treated to prevent HBV transmission (**LoE 3, weak recommendation, strong consensus**).
- In pregnant women with HBV DNA $\geq 200,000$ IU/ml, antiviral therapy should be administered to prevent mother-to-child transmission (specific recommendation see 6.2) (**LoE 1, strong recommendation, strong consensus**).

**HBeAg-pos infection
(phase 1)**



**HBeAg-neg infection
(phase 3)**



Should patients with HBeAg-negative chronic infection be treated?

Individuals with chronic HBeAg-negative infection who generally do not require treatment are those with persistently

Statement

- Patients with HBeAg-negative chronic infection (persistent HBV DNA $< 2,000$ IU/ml, persistently normal ALT, no signs of liver fibrosis) have a low risk of disease progression and transmission and usually do not require immediate antiviral treatment (**strong consensus**).

Recommendations

- Individuals with HBeAg-negative chronic infection and a high risk of HCC should be treated (**LoE 4, strong recommendation, strong consensus**).
- Individuals with HBeAg-negative chronic infection and HBV-related extrahepatic manifestations should be treated (**LoE 4, strong recommendation, strong consensus**).
- Individuals with HBeAg-negative chronic infection who are being considered for immunosuppressive therapy or who are immunocompromised should receive antiviral therapy (see 7.1) to prevent HBV reactivation/hepatitis (**LoE 2, strong recommendation, strong consensus**).
- Selected individuals with HBeAg-negative chronic infection can be treated to prevent HBV transmission (**LoE 4, weak recommendation, consensus**)*.

EASL 2025 Guidelines -Treatment indication for chronic HBV infection

Decomp and ACLF patients

How should patients with HBV infection and decompensated cirrhosis or acute-on-chronic liver failure be managed?

Recommendation

- HBsAg-positive patients with decompensated cirrhosis or acute-on-chronic liver failure **should be treated** with ETV or tenofovir (TDF, TAF), irrespective of HBV DNA levels. PEG-IFN α should not be used in patients with decompensated cirrhosis or ACLF (**LoE 1, strong recommendation, strong consensus**).

HCC patients

Should patients with chronic HBV infection and HCC be treated with antiviral therapy, and if so, how?

Recommendations

- HBsAg-positive patients with HCC **should be treated** with NAs, irrespective of HBV DNA levels (**LoE 2, strong recommendation, strong consensus**).
- TDF is suggested as the preferred NA for tertiary prophylaxis after curative treatment (e.g. surgery or locoablative therapy) for HCC (**LoE 2, weak recommendation, strong consensus**).

HBV/HIV patients

What should be considered when treating patients with HBV/HIV coinfection?

Recommendations

- HBsAg-positive individuals living with HIV should receive anti-HBV treatment regardless of ALT or HBV DNA levels (**LoE 2, strong recommendation, strong consensus**).
- HBV therapy should be given as part of antiretroviral HIV therapy. In HBsAg-positive individuals living with HIV, the antiretroviral therapy should contain tenofovir (TDF or TAF) (**LoE 1, strong recommendation, strong consensus**).
- Treatment monitoring and adjustments should be carried out in accordance with the recommendations for HBV-monoinfected patients, taking into account the HIV coinfection (**LoE 5, strong recommendation, strong consensus**).
- Anti-HBV-containing antiretroviral therapy should not be discontinued in HBV/HIV coinfection due to the risk of HBV rebound and biochemical relapse (**LoE 2, strong recommendation, strong consensus**).

EASL 2025 Guidelines -Treatment indication for chronic HBV infection

HBV and HCV patients

What should be considered when treating HBsAg-positive patients with HBV/HCV coinfection?

Statement

- The indications for anti-HBV treatment are generally the same as those for chronic HBV mono-infection. However, in the context of anti-HCV therapy, there are additional factors to consider (**strong consensus**).

Recommendations

- HBsAg-positive patients with chronic HCV infection should be treated with HCV-specific direct-acting antivirals (**LoE 2, strong recommendation, strong consensus**).
- All HBsAg-positive patients with cirrhosis (even if HBV DNA is undetectable) should receive NA therapy during anti-HCV direct-acting antiviral therapy to prevent HBV reactivation (**LoE 2, strong recommendation, strong consensus**).
- Prophylactic NA treatment to prevent reactivation during anti-HCV direct-acting antiviral treatment can be given in patients not meeting the indication for treatment of chronic HBV mono-infection (e.g. HBV DNA <2,000 IU/ml, normal ALT and absence of advanced fibrosis/cirrhosis) (**LoE 2, weak recommendation, strong consensus**).

HBV and HDV patients

What should be considered when treating patients with HBV/HDV coinfection?

Recommendations

The main recommendations for the treatment of chronic hepatitis delta (including LoE and grade of recommendation) are taken from the EASL clinical practice guidelines on hepatitis D[†].⁶⁴

- All patients with chronic HBV/HDV coinfection (hepatitis delta) should be considered for anti-HDV treatment (LoE 3, strong recommendation)[†].
- Patients with decompensated cirrhosis should be evaluated for liver transplantation (LoE 3, strong recommendation)[†].
- All patients with chronic HBV/HDV coinfection (hepatitis delta) and compensated liver disease, irrespective of whether they have cirrhosis or not, should be considered for treatment with PEG-IFN α or bulevirtide (LoE 2 for

PEG-IFN α and LoE 3 for bulevirtide, strong recommendation)[†].

- The combination of PEG-IFN α and bulevirtide may be considered in patients without PEG-IFN α intolerance or contraindications (LoE 5, weak recommendation)[†].
- NAs should be given in patients with compensated or decompensated cirrhosis (LoE 5, strong recommendation)[†].
- NAs should be given in patients without cirrhosis if HBV DNA levels are $\geq 2,000$ IU/ml (LoE 5, strong recommendation)[†].
- Patients with decompensated liver disease may be treated with bulevirtide monotherapy depending on the individual's risk benefit assessment. If decompensation occurs during therapy with bulevirtide monotherapy, therapy can be continued (**LoE 4, weak recommendation, strong consensus**).

EASL 2025 Guidelines – how to treat CHB

Table 9. Differences between PEG-IFN α and NA therapy.

Features	ETV, tenofovir (TDF, TAF)	PEG-IFN α
Strategy	Preventing disease progression through persistent HBV suppression	Induction of an off-treatment response through finite treatment
Administration	Oral, once daily	Subcutaneous, once weekly
Treatment duration	Long-term	Finite (48 weeks)
Response guided treatment	Criteria for stopping long-term therapy before HBsAg loss (see 4.4)	Stopping rules after 12-24 weeks of therapy (see 4.5)
Side effects	Very low	Moderate to high
Contraindications	Very few (e.g. ETV in pregnancy)	Numerous
Level of viral suppression	High	Low to high, depending on patient profile
HBeAg/anti-HBe seroconversion rates	Initially low, moderate during long-term treatment	Low to high, depending on patient profile
HBsAg loss	Very low	Low, higher compared to NAs
Risk of viral resistance	Very low	Absent

ETV, entecavir; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NAs, nucleos(t)ide analogues; PEG-IFN α , pegylated interferon-alfa.



- *De novo* combination therapy with PEG-IFN α and NAs cannot be generally recommended. PEG-IFN α as an add-on therapy can be considered in selected HBeAg-negative patients undergoing NA therapy with low HBsAg levels (LoE 2, weak recommendation, consensus).*

When to Stop therapy (NUC)

Discontinuation of long-term NUC therapy

- **After HBsAg loss/anti-HBs seroconversion**

- Safe and effective even in cirrhotics, low risk of seroreversion, antiHBs titers?

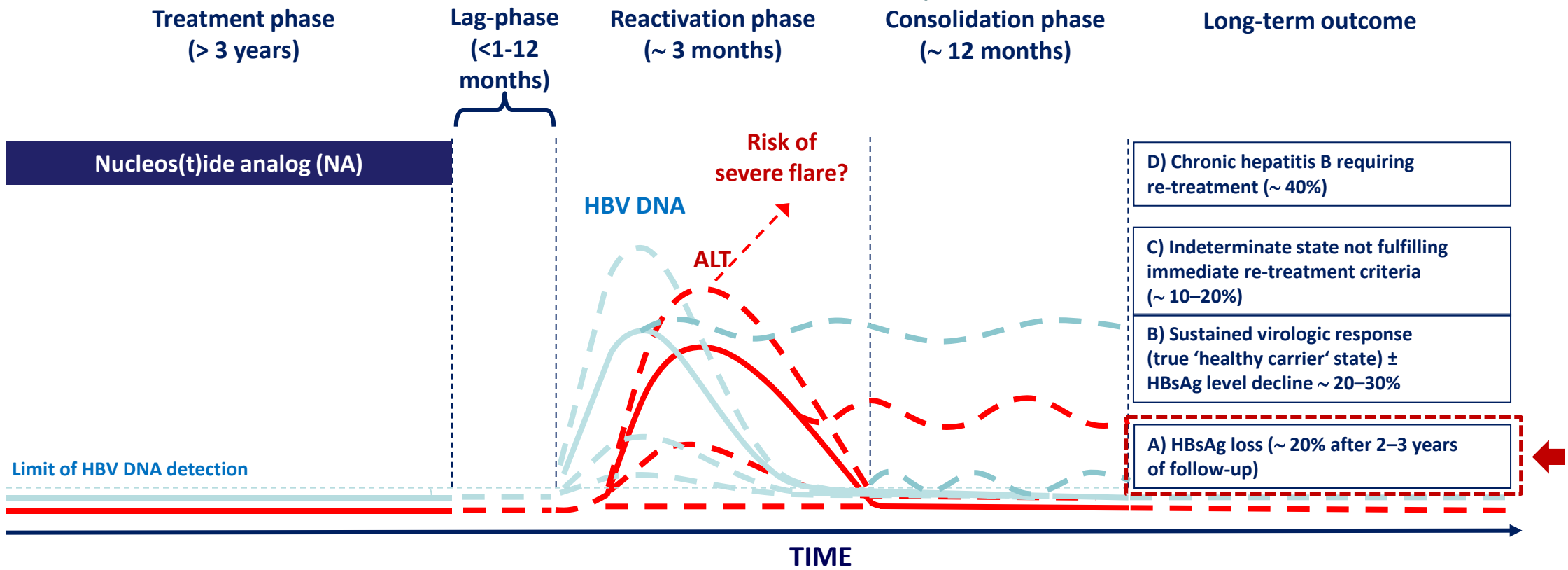
- **Before HBsAg loss**

- **to be discussed.....**but not in patients with cirrhosis at NUC start !!

Stopping NA therapy before HBsAg loss in HBeAg-negative CHB

Potential outcome predictors

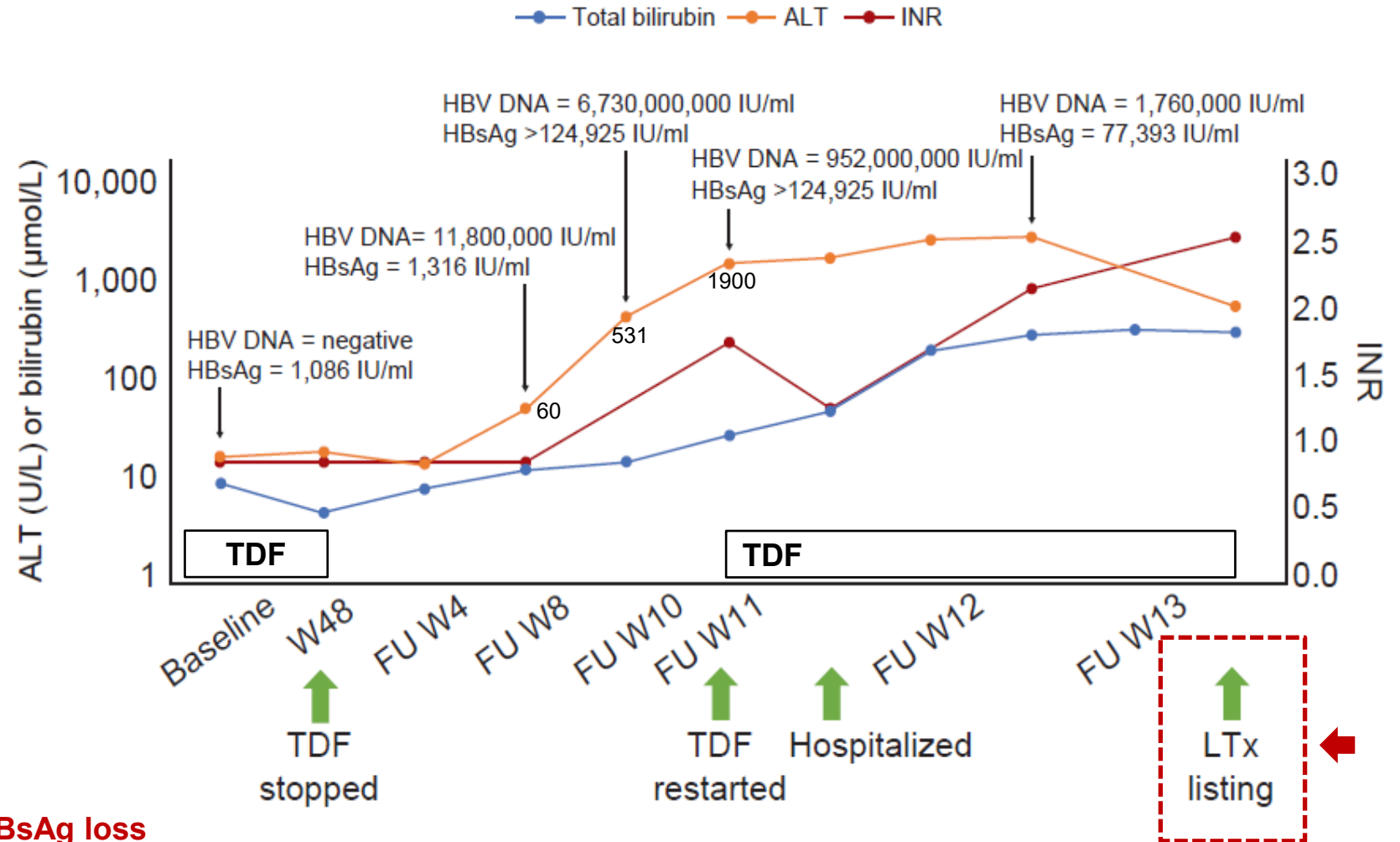
Age, time to undetectable HBV DNA, and duration of viral suppression under NA, HBsAg levels at NA baseline and NA cessation, type of NA (TDF vs. ETV), HBV DNA levels during reactivation phase, re-treatment strategy, and HBV genotype



A case of HBV-induced liver failure in the REEF-2 phase II trial: Implications for finite treatment strategies in HBV cure

Patient profile

- 54 yrs, male (UK)
- HBeAg-neg CHB
- on TDF from 2009
- Fibroscan: 3.6 to 6.1 kPa
- HBV DNA undetectable
- HBsAg: 900 to 3600 IU
- Enrolled in REEF 2 study
- Control group (no active therapy)
- NUC discontinuation group



Conclusions

- Potential risk of NUC stop before HBsAg loss
- NUC rescue therapy protocol modified (HBV DNA >5 log IU/ml)

Management during and after NUC discontinuation: 1-year simulation

TESTING/VISITS	CONTINUE NUC (on-therapy)	STOP NUC (off-therapy)
HBsAg/HBV DNA (HBeAg)	Every 24-48 weeks	Every 4 weeks up to week 24 Every 8-12 weeks after week 24
Liver tests (Bil, AST, ALT....)	Every 24-48 weeks	Every 4 weeks up to week 24 Every 8-12 weeks after week 24
Liver Ultrasound	Every 48 weeks	Every 24-48 weeks
Fibroscan	Every 48-96 weeks	Every 48-96 weeks
Outpatient visits	Every 24-48 weeks	Every 4 weeks up to week 24 Every 8-12 weeks after week 24
Patient compliance	Low	High
Doctor compliance	Low	High
Doctor experience	Low	High
Overall cost	Low	High
Overall committment/time	Low	High

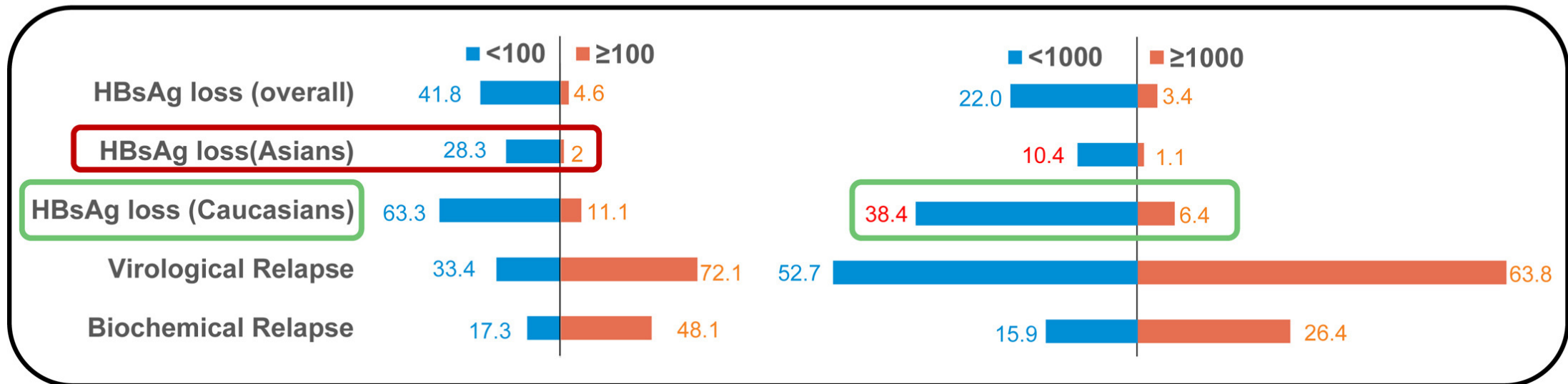
48 weeks simulation: on- vs off-NUC therapy

Stopping NUC in Chronic Hepatitis B Using HBsAg Thresholds

A Meta-Analysis and Meta Regression

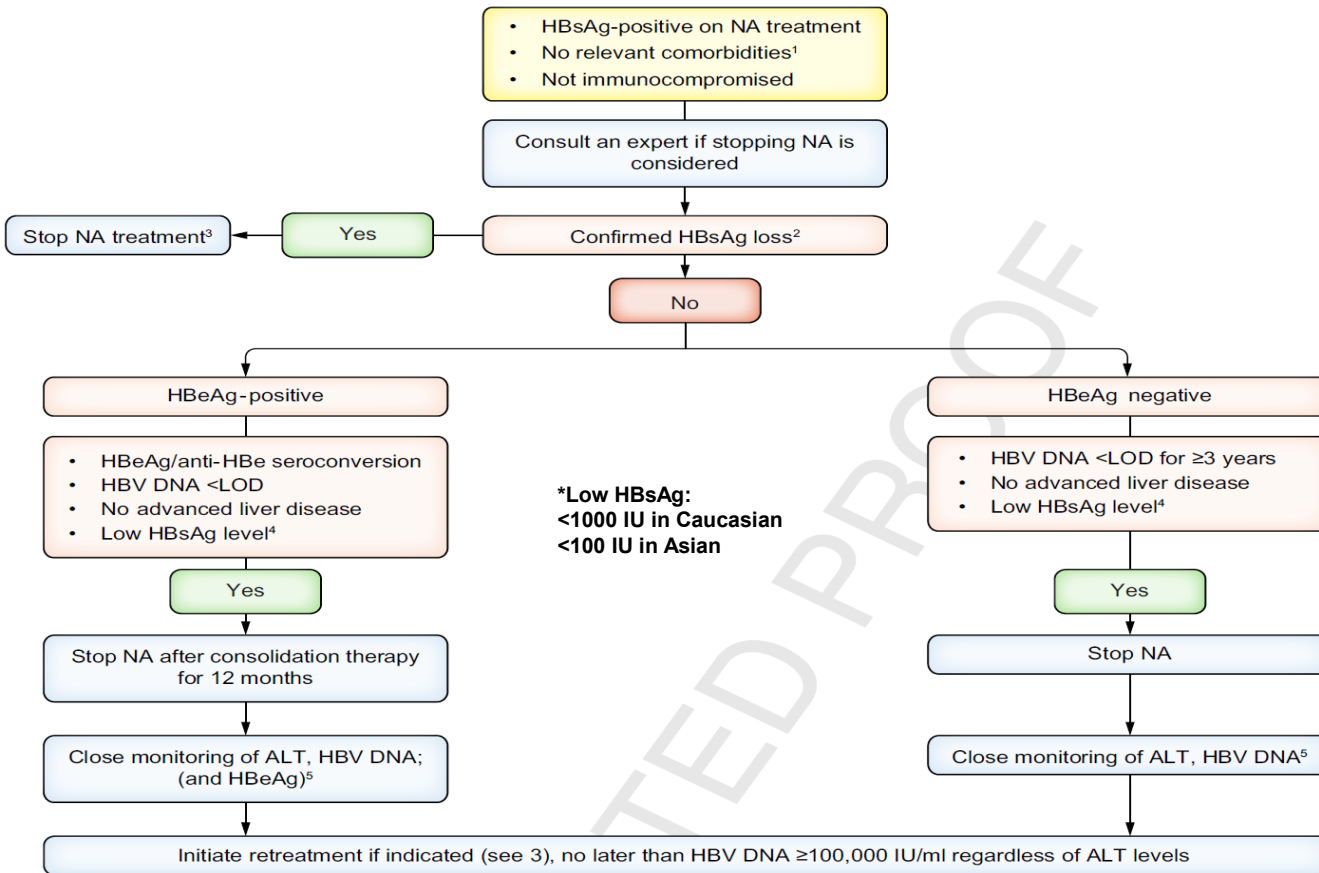
- Systematic review and meta-analysis of 24 articles, 7 non-Asian
- 3,732 patients followed for 9.8-111.6 months off NA
- Race, follow up duration, EOT HBsAg only explained 43% and 63% of variability in virological relapse and biochemical relapse, respectively
- 36 (1%) had hepatic decompensation of whom 19 did not have cirrhosis

qHBsAg thresholds for stopping Nucleoside Analogue therapy



EASL 2025 Guidelines – NUC discontinuation in CHB

When can antiviral therapy for hepatitis B with NAs be stopped?



Recommendations

- Antiviral therapy with NAs should only be discontinued after consultation with a physician experienced in the treatment of hepatitis B and if close monitoring is guaranteed. HBsAg levels, HBeAg status, comorbidities, duration of HBV DNA suppression, stage of liver fibrosis in addition to patient understanding and preference should be taken into account (**LoE 2, strong recommendation, strong consensus**).
- Antiviral therapy with NAs should be stopped after confirmed HBsAg loss with or without anti-HBs seroconversion in the absence of coexisting risk factors (**LoE 2, strong recommendation, consensus**).
- When considering NA discontinuation in HBsAg-positive individuals, HBsAg levels should be used to select patients (**LoE 2, strong recommendation, strong consensus**).

• In HBeAg-positive patients without advanced liver disease, antiviral therapy with NAs can be stopped 12 months after confirmed HBeAg/anti-HBe seroconversion and undetectable HBV DNA if close monitoring is guaranteed after the end of therapy (**LoE 2, weak recommendation, consensus**)*.

• In selected HBeAg-negative patients without advanced liver disease, NA therapy can be discontinued before HBsAg loss if HBV DNA has been undetectable for at least 3-4 years, HBsAg level is low (for values see comments below), and close monitoring is guaranteed after the end of therapy (**LoE 1-2, weak recommendation, consensus**)*.

• In addition to HBsAg level, HBcrAg and HBV RNA level can be used to further improve the patient stratification before discontinuing therapy (**LoE 3, weak recommendation, consensus**)*.

Fig. 2. Algorithm for stopping NA treatment. ¹HCC, decompensated cirrhosis, HIV. ²HBsAg loss is confirmed on two occasions 6 months apart. ³In patients with compensated cirrhosis, we suggest discontinuing NA therapy only after confirmed seroconversion to anti-HBs or following HBsAg loss with at least 12 months of consolidation therapy. ⁴HBsAg <1,000 IU/ml for Caucasians; <100 for Asians (data more robust in HBeAg-negative); HBcrAg, HBV RNA can be used to further improve stratification. ⁵Monitoring at least monthly for the first 6 months, followed by every 3 months for 12–24 months, considering earlier relapse with tenofovir vs. entecavir. ALT, alanine aminotransferase; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LOD, limit of detection; NA, nucleos(t)ide analogue.

Stopping NA before HBsAg loss



HBeAg-, no cirrhosis, ≥ 3 yr NA,
 ≥ 1 yr undetectable HBV DNA,
agree to close monitoring
Test qHBsAg

qHBsAg < 1000 IU/mL for Caucasian
or < 100 IU/mL for Asian
Test HBcrAg and/or HBV RNA

qHBsAg > 1000 IU/mL for Caucasian
or > 100 IU/mL for Asian

HBcrAg and/or
HBV RNA low/neg
Can try to stop NA

HBcrAg and/or
HBV RNA pos/high
DO NOT STOP NA

**DO NOT
STOP NA**

**~30% Caucasian
~10% Asian**

**~70% Caucasian
~90% Asian**

When to start/stop HBV therapy - Take home messages

When to start antiHBV therapy ?

- The only individuals I **DO NOT TREAT** are F0-2 patients with HBV DNA <2000 IU and persistently normal ALT levels

NUC discontinuation before HBsAg loss in HBeAg neg CHB (in clinical practice):

- I usually **DO NOT STOP NUC** before HBsAg loss.... but its possible and effective in selected patients....
- But management is complicated/demanding/expensive....
- And probability to clear HBsAg is limited to a subset.....
- And predictors of HBsAg loss are not well defined (qHBsAg <1000/100 IU?).....
- And safety could be a problem (only if HBcrAg/HBV RNA negative ?...).....
- And current NUC therapy is very effective/cheap/safe/easy to manage....
- And new therapeutics under development may clear HBsAg.....

Thank You for Your Attention!



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