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EASL HBV guidelines 2017

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Disclosures

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- BMS, ROCHE, GILEAD SCIENCES, GSK, ABBVIE, MSD, ARROWHEAD, ALNYLAM, JANSSEN

Clinical Practice Guidelines

EASL JOURNAL OF HEPATOLOGY

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection☆

European Association for the Study of the Liver*

Chair: Pietro Lampertico

Panel members:
Kosh Agarwal, Thomas Berg, Maria Buti, Harry L.A. Janssen, George Papatheodoridis, Fabien Zoulim; EASL Governing Board representative: Frank Tacke

Reviewers:
EASL Governing Board, Maurizia Brunetto, Henry Chan, Markus Cornberg

HBV clinical practice guidelines - topics

1) Goals of therapy
2) Endpoints of therapy
3) Indications for treatment
4) Monitoring of patients currently not treated
5) Treatment strategies
6) Definition of response
7) NA monotherapy (efficacy, safety, long-term outcome…….)
8) Peg-IFNalpha monotherapy (efficacy, safety, long-term outcome…)
9) Combination therapy (NA+NA, NA + PEG-IFN)
10) Patients with decompensated cirrhosis
11) Prevention of HBV recurrence after LT
12) Treatment of special populations (coinfection, acute hepatitis, children….)

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Natural history of HBV and treatment indications

PHASE	1	2	3	4
New terminology	**HBeAg positive Chronic *infection***	**HBeAg positive Chronic hepatitis**	**HBeAg negative Chronic *infection***	**HBeAg negative Chronic hepatitis**
Old terminology	***Immune tolerant***	***HBeAg-positive CHB***	***Inactive carrier***	***HBeAg-negative CHB***
HBsAg	High	High/Intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10E7 IU/mL	10E4-10E7 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**	No, very low	**Moderate to high**
Treatment	Not indicated***	**Indicated**	Not indicated	**Indicated**

* HBV-DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis

** Persistently or intermittently

*** Treatment is indicated in some patients

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Natural history of HBV and treatment indications

PHASE	1	2	3	4	5
New Terminology	HBeAg positive Chronic *infection*	HBeAg positive Chronic hepatitis	HBeAg negative Chronic *infection*	HBeAg negative Chronic hepatitis	Resolved HBV infection
Old terminology	*Immune tolerant*	*HBeAg-positive CHB*	*Inactive carrier*	*HBeAg-negative CHB*	HBsAg negative/anti-HBcore positive
HBsAg	High	High/Intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	>10E7 IU/mL	10E4-10E7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL	<10 IU/ml[a]
ALT	Normal	Elevated	Normal	Elevated**	Normal
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe	None[b]
Disease progression	Low	**Moderate to high**	No, very low	**Moderate to high**	None[b]
Treatment	Not indicated***	**Indicated**	Not indicated	**Indicated**	Not indicated but prophylaxis for selected cases

* HBV-DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis

** Persistently or intermittently: *** Treatment is indicated in some patients; [a] in >95% of patients but HBV-DNA frequently detectable in the liver; [b] residual HCC risk only if cirrhosis has developed before HBsAg loss

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Indications for treatment

Recommendations:

1) **All patients with HBeAg-positive or -negative chronic hepatitis B**, defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis, **should be treated**. (Evidence level I, grade of recommendation 1)

2) Patients with compensated or decompensated **cirrhosis need treatment**, with any detectable HBV DNA level and regardless of ALT levels. (Evidence level I, grade of recommendation 1)

3) Patients with **HBV DNA >20,000 IU/ml and ALT >2xULN should start treatment regardless of the degree of fibrosis**. (Evidence level II-2, grade of recommendation 1)

4) Patients with **HBeAg-positive chronic HBV infection**, defined by persistently normal ALT and high HBV DNA levels, **may be treated** if they are older than 30 years regardless of the severity of liver histological lesions. (Evidence level III, grade of recommendation 2)

5) Patients with HBeAg-positive or HBeAg-negative **chronic HBV infection** and family history of HCC or cirrhosis and extrahepatic manifestations **can be treated** even if typical treatment indications are not fulfilled. (Evidence level III, grade of recommendation 2)

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Natural history of HBV and treatment indications

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New terminology	**HBeAg positive Chronic *infection***	**HBeAg positive Chronic hepatitis**	**HBeAg negative Chronic *infection***	**HBeAg negative Chronic hepatitis**
Old terminology	***Immune tolerant***	***HBeAg-positive CHB***	***Inactive carrier***	***HBeAg-negative CHB***
HBsAg	High	High/Intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10E7 IU/mL	10E4-10E7 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**	No, very low	**Moderate to high**
Treatment	Not indicated***	**Indicated**	Not indicated	**Indicated**

* HBV-DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis

** Persistently or intermittently

*** Treatment is indicated in some patients

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Endpoints of therapy

Recommendations:

1) The induction of **long-term suppression of HBV DNA** levels represents the **main endpoint** of all current treatment strategies. (Evidence level I, grade of recommendation 1)

2) The induction of **HBeAg loss,** with or without anti-HBe seroconversion, in HBeAg-positive CHB patients is a **valuable endpoint**, as it often represents a partial immune control of the chronic HBV infection. (Evidence level II-1, grade of recommendation 1)

3) A biochemical response defined as **ALT normalization** should be considered as an **additional endpoint**, which is achieved in most patients with long-term suppression of HBV replication. (Evidence level II-1, grade of recommendation 1)

4) **HBsAg loss**, with or without anti-HBs seroconversion, is an **optimal endpoint**, as it indicates profound suppression of HBV replication and viral protein expression. (Evidence level II-1, grade of recommendation 1)

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Main concepts and features of current treatment strategies for HBV

Features	PegIFNα	ETV, TDF, TAF
Route of administration	Subcutaneous injections	Oral
Treatment duration	48 weeks	Long-term until HBsAg loss (stopping NA after some years might be considered in selected cases)[1]
Tolerability	Low	High
Long-term safety concerns	Very rarely persistence of on-treatment adverse events (psychiatric, neurological, endocrinological)	Probably not (uncertainties regarding kidney function, bone diseases for some NA)
Contraindications	Many (*i.e.*, decompensated disease, co-morbidities etc.)	None (dose adjustment according to eGFR[2])
Strategy	Induction of a long-term immune control by finite treatment	Stopping hepatitis and disease progression by inhibiting viral replication
Level of viral suppression	Moderate (variable response pattern)	Universally high
Effect on HBeAg loss	Moderate, depending on baseline characteristics	Low in the first year, increases to moderate during long-term treatment
Effect on HBsAg levels	Variable, depending on baseline characteristics (overall higher as compared to NA)	Low: slowly increases with treatment time in HBeAg-positive patients[3]; usually very low in HBeAg-negative patients
Risk of relapse after treatment cessation	Low for those with sustained response 6–12 months after therapy	Moderate if consolidation treatment provided after HBeAg seroconversion. High for HBeAg-negative disease
Early stopping rules	Yes	No
Risk of viral resistance development	No	Minimal to none[4]

1. See section on 'Treatment strategies'.
2. Dose adjustments in patients with eGFR <50 ml/min are required for all NA, except for TAF (no dose recommendation for TAF in patients with CrCl <15 ml/min who are not receiving haemodialysis).
3. A plateau in serologic responses has been observed beyond treatment year 4.
4. So far no TDF or TAF resistance development has been detected.

Table 2

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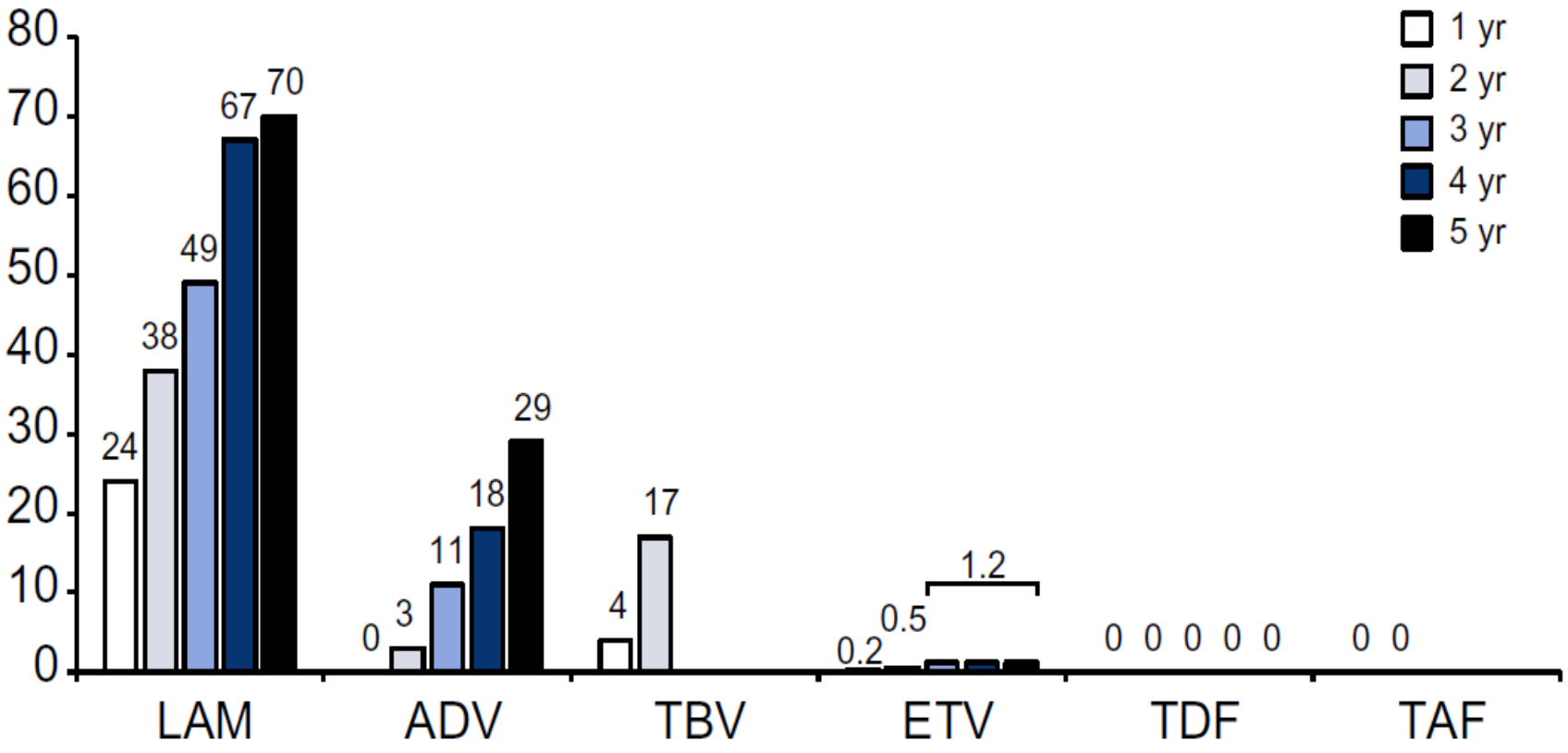
Cumulative incidence of HBV resistance for NA in pivotal trials in nucleos(t)ide-naïve patients with CHB

Collation of currently available data – not from head-to head studies



Note: No evidence of resistance has been shown after 8 years of TDF treatment.

Figure 3

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Indications for selecting ETV or TAF over TDF*

1. Age >60 year
2. Bone disease
Chronic steroid use or use of other medications that worsen bone density
History of fragility fracture
Osteoporosis
3. Renal alteration**
eGFR <60 min/ml/1.73 m^2
Albuminuria >30 mg or moderate dipstick proteinuria
Low phosphate (<2.5 mg/dl)
Hemodialysis

* TAF should be preferred to ETV in patients with previous exposure to nucleoside analogues.

** ETV dose needs to be adjusted if eGFR <50 ml/min; no dose adjustment of TAF is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) 15 ml/min or in patients with CrCl <15 ml/min who are receiving haemodialysis.

Table 5

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NA discontinuation

Recommendations:

1) NAs **should be discontinued after confirmed HBsAg loss**, with or without anti-HBs seroconversion. (Evidence level II-2, grade of recommendation 1).

2) NAs **can be discontinued in non-cirrhotic HBeAg positive** CHB patients **who achieve stable HBeAg seroconversion** and undetectable HBV DNA and who complete at least 12 months of consolidation therapy. Close post-NA monitoring is warranted. (Evidence level II-2, grade of recommendation 2)

3) Discontinuation of NAs in selected non-cirrhotic HBeAg-negative patients who have achieved long-term (3 years) virological suppression under NA(s) **may be considered** if close post-NA monitoring can be guaranteed. (Evidence level II-2, grade of recommendation 2)

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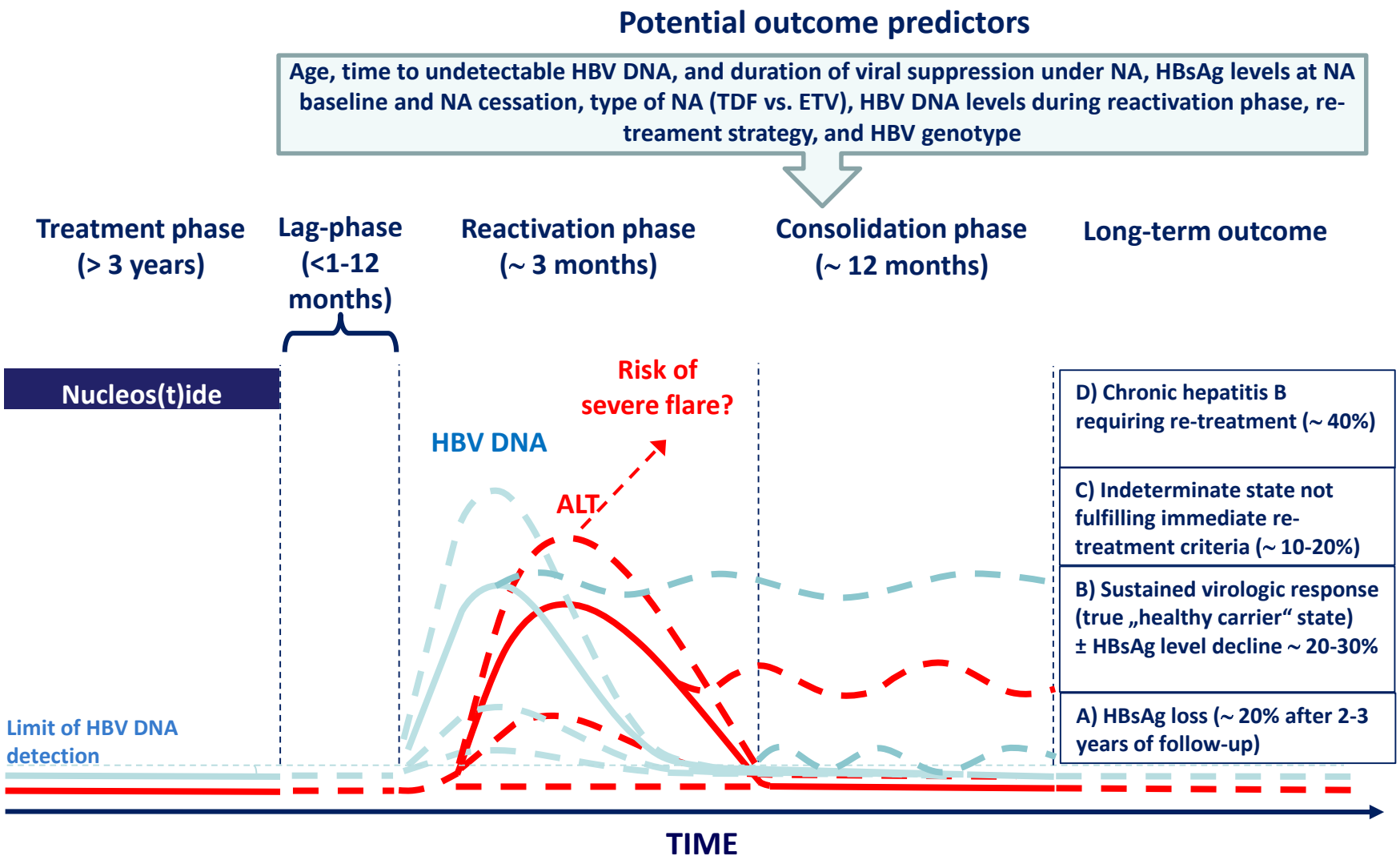
NUC discontinuation in HBeAg negative CHB before HBsAg loss



Lampertico P and Berg T, Hepatology 2018 in press

Management of HDV co-infected patients

Recommendations:

1) **PegIFNa** for at least 48 weeks is the **current treatment of choice** in HDV-HBV co-infected patients with compensated liver disease. (Evidence level I, grade of recommendation 1)

2) In HDV-HBV co-infected patients with **ongoing HBV DNA replication, NA therapy should be considered**. (Evidence level II-2, grade of recommendation 1)

3) PegIFNa treatment **can be continued until week 48 irrespective** of on-treatment response pattern if well tolerated. (Evidence level II-2, grade of recommendation 2)

Management of HCV coinfected patients

Recommendations:

1) Treatment of HCV with direct-acting antivirals (DAAs) may cause reactivation of HBV. Patients fulfilling the standard criteria for HBV treatment **should receive NA treatment**. **(Evidence level II, grade of recommendation 1)**

2) HBsAg-positive patients undergoing DAA therapy **should be considered for concomitant NA prophylaxis** until week 12 post DAA, and monitored closely. **(Evidence level II-2, grade of recommendation 2)**

3) HBsAg-negative, anti-HBc positive patients undergoing DAA **should be monitored** and tested for HBV reactivation in case of ALT elevation. **(Evidence level II, grade of recommendation 1)**

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Prevention of HBV recurrence after liver transplantation

Recommendations:

1) All **patients on the transplant waiting list** with HBV related liver disease **should be treated with NA**. (Evidence level II, grade of recommendation 1)

2) **Combination** of hepatitis B immunoglobulin (HBIG) and a potent NA **is recommended** after liver transplantation for the prevention of HBV recurrence. (Evidence level II-1, grade of recommendation 1)

3) Patients with a low risk of recurrence **can discontinue HBIG** but need continued monoprophylaxis with a potent NA. (Evidence level II-1, grade of recommendation 2)

4) HBsAg-negative patients receiving livers from donors with evidence of past HBV infection (anti-HBc positive) are at risk of HBV recurrence and should receive antiviral prophylaxis with a NA. (Evidence level II-2, grade of recommendation 1)

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Pregnancy and HBV

Recommendations:

1) **Screening** for HBsAg in the first trimester of pregnancy is strongly recommended. (Evidence level 1, grade of recommendation 1)
2) **In a woman of childbearing age** without advanced fibrosis who plans a pregnancy in the near future, it may be prudent to delay therapy until the child is born. (Evidence level II-2, grade of recommendation 2)
3) **Pregnant women with CHB and advanced fibrosis or cirrhosis**, therapy with TDF is recommended. (Evidence level II-2, grade of recommendation 1)
4) **In pregnant women already on NA therapy**, TDF should be continued while ETV or other NA should be switched to TDF. (Evidence level II-2, grade of recommendation 1)
5) **In all pregnant women with high HBV DNA levels** (>200,000 IU/ml) or HBsAg levels >4 log10 IU/ml, antiviral prophylaxis with TDF should start at week 24–28 of gestation and continue for up to 12 weeks after delivery. (Evidence level 1, grade of recommendation 1)
6) **Breast feeding is** not contraindicated in HBsAg positive untreated women or on TDF-based treatment or prophylaxis. (Evidence level III, grade of recommendation 2)

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Patients undergoing immunosuppressive therapy or chemotherapy

Recommendations:

1) **All candidates** for chemotherapy and immunosuppressive therapy **should be tested** for HBV markers prior to immunosuppression. (Evidence level I, grade of recommendation 1)

2) **All HBsAg-positive patients** should receive ETV or TDF or TAF as treatment or prophylaxis. Evidence level II-2, grade of recommendation 1)

3) **HBsAg-negative, anti-HBc positive** subjects should receive anti-HBV prophylaxis if they are at high risk of HBV reactivation. (Evidence level II-2, grade of recommendation 1)

Algorithm for the management of HBV infection

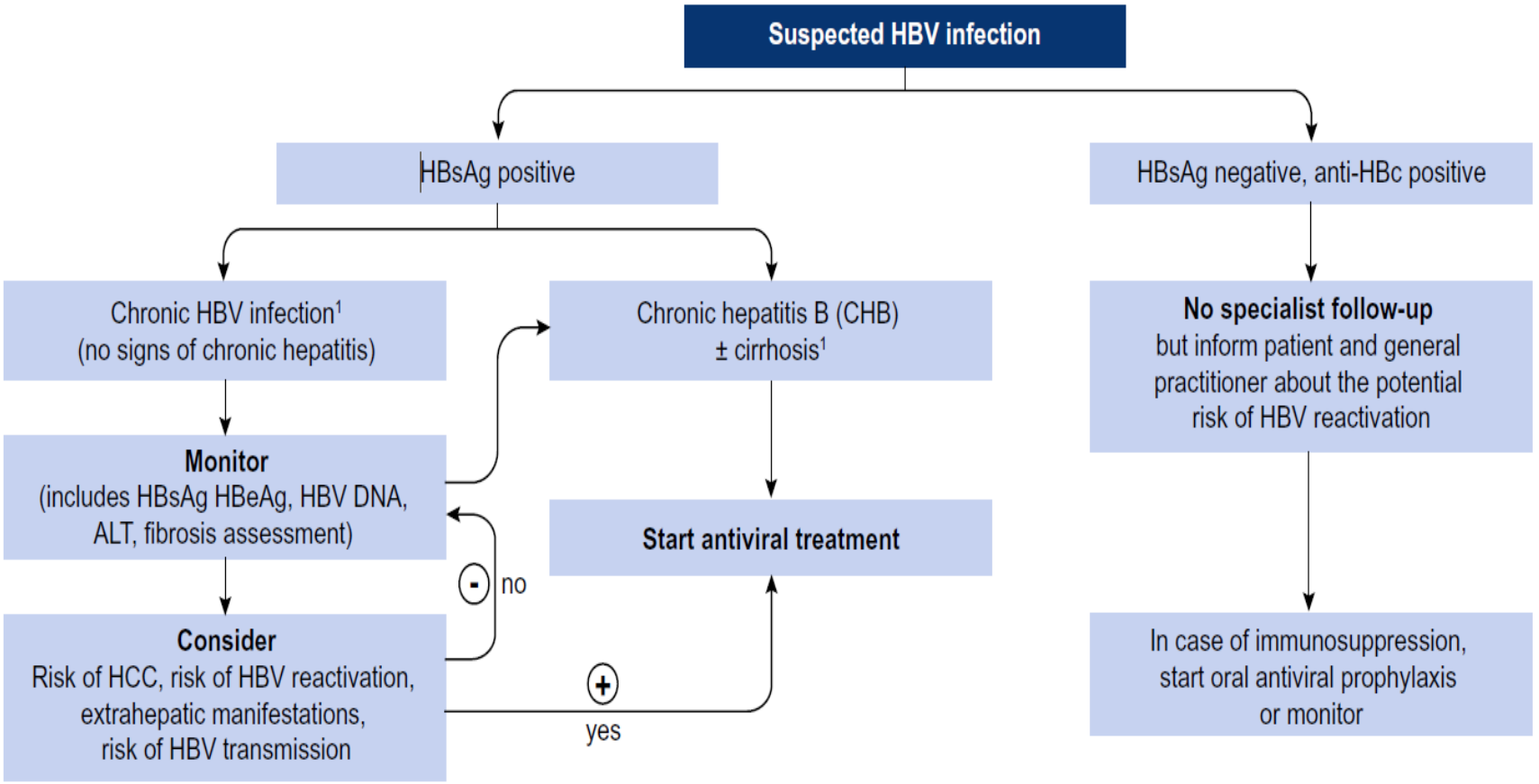

Figure 2

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Standard and New markers for HBV

Standard markers:

- qHBsAg
- HBeAg/anti-HBe
- HBV-DNA levels
- Anti-HBc

New markers:*

- ultra sens qHBsAg
- HBeAg levels
- ultra sens HBV-DNA
- Anti-HBc levels
- HBcrAg
- HBV-RNA levels
- Different HBsAg proteins

* No commercially available assays available

The "future" of HBV management

- New biomarkers (cccDNA, HBcrAg, HBV-RNA)
- Future treatment options for HBV
- Future treatment options for HDV

Unresolved issues and unmet needs

1) When to start antiviral therapy in patients with HBeAg-positive chronic HBV infection
2) Stopping rules for HBeAg-negative patients treated with NA
3) Retreatment criteria after NA discontinuation
4) How to accelerate HBsAg decline in long-term NA treated patients?
5) Better baseline or on-treatment predictors of sustained treatment in patients treated with PegIFNa
6) Definition of the residual risk of HCC in patients on long-term
7) NA therapy and impact on surveillance
8) Unmet need: new treatments with finite duration and high cure rates
9) How to define a cure of HBV infection? Definition of novel endpoints
10) Biomarkers for the cure of infection and for the cure of the liver disease

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Back-up slides

Phase 5 – "resolved" HBV infection

- **HBsAg neg, anti-HBc pos** (anti-HBs pos/neg, anti-HBe pos/neg)
- Undetectable serum HBV-DNA in >90%, normal ALT
- Long-lasting persistence of HBV genomes in the liver with active HBV replication in few liver cells
- Different nomenclature partially overlapping (Occult HBV Infection, recovery phase, functional cure……..)
- Outcome of different clinical situations (acute HBV, spontaneous or drug-induced HBsAg loss, inactive cirrhosis…….)
- Residual HCC risk (age and gender)
- HBV may reactivate during immunosuppression

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