Сеченовский Университет

HBV TREATMENT GUIDELINES AND GUIDANCE

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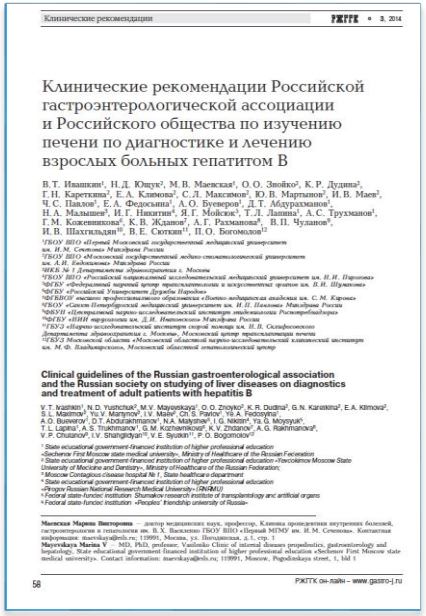
Department of internal, occupational diseases and rheumatology

HBV GUIDELINES AND GUIDANCE

РГА и РОИП-2014



Клинические рекомендации РЖГГК ○ 3, 2014

Клинические рекомендации Российской гастроэнтерологической ассоциации и Российского общества по изучению печени по диагностике и лечению взрослых больных гепатитом В

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APASL-2015

Hepatol Int (2016) 10:1–98
DOI 10.1007/s12072-015-9675-4

GUIDELINES

Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update

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Received: 20 May 2015 / Accepted: 14 September 2015/Published online: 13 November 2015
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Abstract Worldwide, some 240 million people have chronic hepatitis B virus (HBV), with the highest rates of infection in Africa and Asia. Our understanding of the natural history of HBV infection and the potential for therapy of the resultant disease is continuously improving. New data have become available since the previous APASL guidelines for management of HBV infection were published in 2012. The objective of this manuscript is to update the recommendations for the optimal management of chronic HBV infection. The 2015 guidelines were developed by a panel of Asian experts chosen by the APASL. The clinical practice guidelines are based on evidence from existing publications or, if evidence was unavailable, on the experts' personal experience and opinion after deliberations. Manuscripts and abstracts of important meetings published through January 2015 have

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EASL-2017

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

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

European Association for the Study of the Liver *

Summary

Hepatitis B virus (HBV) infection remains a global public health problem with changing epidemiology due to several factors including vaccination policies and migration. This Clinical Practice Guideline presents updated recommendations for the optimal management of HBV infection. Chronic HBV infection can be classified into five phases: (1) HBeAg-positive chronic infection, (II) HBeAg-positive chronic hepatitis, (III) HBeAg-negative chronic infection, (IV) HBeAg-negative chronic hepatitis and (V) HBsAg-negative phase. All patients with chronic HBV infection are at increased risk of progression to cirrhosis and hepatocellular carcinoma (HCC), depending on host and viral factors. The main goal of therapy is to improve survival and quality of life by preventing disease progression, and consequently HCC development. The induction of long-term suppression of HBV replication represents the main endpoint of current treatment strategies, while HBsAg loss is an optimal endpoint. The typical indication for treatment requires HBV DNA >2,000 IU/mL, elevated ALT and/or at least moderate histological lesions, while all cirrhotic patients with detectable HBV DNA should be treated. Additional indications include the prevention of mother to child transmission in pregnant women with high viremia and prevention of HBV reactivation in patients requiring immunosuppression or chemotherapy. The long-term administration of a potent nucleos(t)ide analogue with high barrier to resistance, i.e., entecavir, tenofovir disoproxil or tenofovir alafenamide, represents the treatment of choice. Pegylated interferon-alfa treatment can also be considered in mild to moderate chronic hepatitis B patients. Combination therapies are not generally recommended. All patients should be monitored for risk of disease progression and HCC. Treated patients should be monitored for therapy response and adherence. HCC remains the major concern for treated chronic hepatitis B patients. Several subgroups of patients with HBV infection require specific focus. Future treatment strategies to achieve 'cure' of disease and new biomarkers are discussed.
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Keywords: Hepatitis B; DAA; guidelines; Treatment; Interferon; Entecavir; Tenofovir; TDF; HBsAg; Hepatocellular carcinoma; HBV DNA; HBV reactivation; Mother to child transmission.
Received 23 March 2017; accepted 23 March 2017
* Clinical practice guidelines panel: Chair: Fabio Lanzoprazi; Panel members: Rosh Agarwal, Thomas Berg, Maria Buti, Harry L.A. Janssen, George Papatheodoridis, Fabien Zoulim; EASL Governing Board representative: Ramon Bataller
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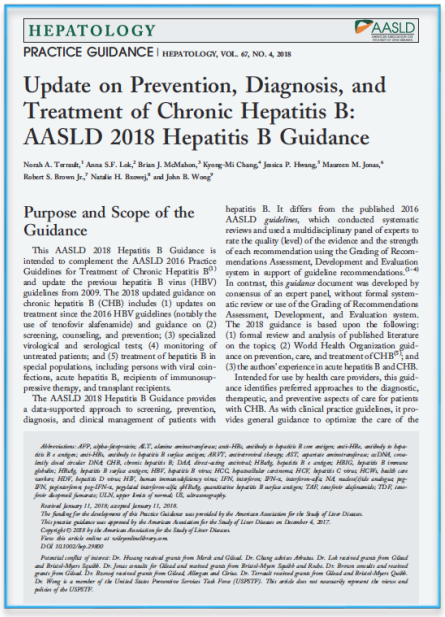
AASLD-2018



HEPATOLOGY

AASLD

PRACTICE GUIDANCE | HEPATOLOGY, VOL. 67, NO. 4, 2018

Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance

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Purpose and Scope of the Guidance

This AASLD 2018 Hepatitis B Guidance is intended to complement the AASLD 2016 Practice Guidelines for Treatment of Chronic Hepatitis B[1] and update the previous hepatitis B virus (HBV) guidelines from 2009. The 2018 updated guidance on chronic hepatitis B (CHB) includes (1) updates on treatment since the 2016 HBV guidelines (notably the use of tenofovir alafenamide) and guidance on (2) screening, counseling, and prevention; (3) specialized virological and serological tests; (4) monitoring of untreated patients; and (5) treatment of hepatitis B in special populations, including persons with viral coinfections, acute hepatitis B, recipients of immunosuppressive therapy, and transplant recipients.

The AASLD 2018 Hepatitis B Guidance provides a data-supported approach to screening, prevention, diagnosis, and clinical management of patients with hepatitis B. It differs from the published 2016 AASLD *guidelines*, which conducted systematic reviews and used a multidisciplinary panel of experts to rate the quality (level) of the evidence and the strength of each recommendation using the Grading of Recommendations Assessment, Development and Evaluation system in support of guideline recommendations.[2–4] In contrast, this *guidance* document was developed by consensus of an expert panel, without formal systematic review or use of the Grading of Recommendations Assessment, Development, and Evaluation system. The 2018 guidance is based upon the following: (1) formal review and analysis of published literature on the topics; (2) World Health Organization guidance on prevention, care, and treatment of CHB[5,6] and (3) the authors' experience in acute hepatitis B and CHB.

Intended for use by health care providers, this guidance identifies preferred approaches to the diagnostic, therapeutic, and preventive aspects of care for patients with CHB. As with clinical practice guidelines, it provides general guidance to optimize the care of the

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B e antigen; anti-HBs, antibody to hepatitis B surface antigen; ART, antiretroviral therapy; AST, aspartate aminotransferase; cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; DAA, direct-acting antiviral; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HCWs, health care workers; HDV, hepatitis D virus; HIV, human immunodeficiency virus; IFN, interferon; IFN-α, interferon-alfa; NA, nucleos(t)ide analogue; peg-IFN, pegylated interferon-alfa; qHBsAg, quantitative hepatitis B surface antigen; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limits of normal; US, ultrasonography.

Received January 11, 2018; accepted January 11, 2018.

The funding for the development of this Practice Guidance was provided by the American Association for the Study of Liver Diseases.

This practice guidance was approved by the American Association for the Study of Liver Diseases on December 4, 2017.

View this article online at wileyonlinelibrary.com.
DOI: 10.1002/hep.29800

Potential conflict of interest: Dr. Hwang received grants from Merck and Gilead. Dr. Chang advises Abbvie. Dr. Lok received grants from Gilead and Bristol-Myers Squibb. Dr. Jonas consults for Gilead and received grants from Bristol-Myers Squibb and Roche. Dr. Brown consults and received grants from Gilead. Dr. Bzowej received grants from Gilead, Allergan and Cerus. Dr. Terrault received grants from Gilead and Bristol-Myers Squibb. Dr. Wong is a member of the United States Preventive Services Task Force (USPSTF). This article does not necessarily represent the views and policies of the USPSTF.

HBV GUIDELINES AND GUIDANCE

* Who needs to be treated and why?
* How to treat and when to stop?

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Who needs to be treated and why?

Non-cirrhotic patients

* Elevated ALT levels
  - [EASL, APASL]: >40 IU/ml;
  - [AASLD]: >35 IU/ml (male) and >25 IU/ml (female);

Who needs to be treated and why?

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  - [EASL, APASL]: >40 IU/ml;
  - [AASLD]: >35 IU/ml (male) and >25 IU/ml (female);

AASLD ALT value

For healthy persons:

- <31 IU/ml (for male)
- <19 IU (for female)

For treatment decisions:

- >35 IU/ml (for male)
- >25 (for female)

APASL ALT value definition

ULN is 40 IU/ml

- Low normal (≤0.5 ULN)
- High normal (>0.5 and <1 ULN)
- Minimally raised (>1 and<2 ULN)
- Raised (≥2 ULN)

EASL ALT value definition

ULN is 40 IU/ml

Who needs to be treated and why?

Non-cirrhotic patients

* Elevated ALT levels
  - [EASL, APASL]: >40 IU/ml;
  - [AASLD-2018]: >35 IU/ml (male) and >25 IU/ml (female);
* HBV DNA levels
  - [EASL]: >2000 IU/ml;
  - [AASLD, APASL]:
    - >20000 IU/ml (for HBeAg-pos)
    - >2000 IU/ml (for HBeAg-neg);

Who needs to be treated and why?

Non-cirrhotic patients

* Elevated ALT levels
  - [EASL, APASL]: >40 IU/ml;
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* HBV DNA levels
  - [EASL]: >2000 IU/ml;
  - [AASLD, APASL]: >20000 IU/ml (for HBeAg-pos) and >2000 IU/ml (for HBeAg-neg);
* Severe inflammation (A2 or A3) or significant fibrosis (≥F2) [Liver biopsy by METAVIR]
  - [EASL]: Liver stiffness **>9 kPa** (for normal ALT) or **>12 kPa** (for elevated ALT but below 5x ULN);
  - [APASL]: Liver stiffness **≥8 kPa** or APRI≥1.5;
  - [AASLD]: Liver stiffness cut-off value not indicated (F≥2)

Who needs to be treated and why?

* Elevated ALT levels
  - [EASL, APASL]: >40 IU/ml;
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  - [AASLD]: Liver stiffness cut-off value not indicated (F≥2)

Patients with cirrhosis should be treated if any detectable HBV DNA, regardless of ALT level

Indications for treatment

Primarily based on the combination of 3 criteria

* *HBV DNA, serum ALT and severity of liver disease*

Recommendations	Grade of evidence	Grade of recommendation
Should be treated		
• Patients with HBeAg-positive or -negative chronic hepatitis B*	I	1
• Patients with cirrhosis, any detectable HBV DNA, regardless of ALT level	I	1
• Patients with HBV DNA >20,000 IU/mL and ALT >2x ULN, regardless of severity of histological lesions	II-2	1
May be treated		
• Patients with HBeAg-positive chronic HBV infection† >30 years old, regardless of severity of liver histological lesions	III	2
Can be treated		
• Patients with HBeAg-positive or -negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations‡	III	2

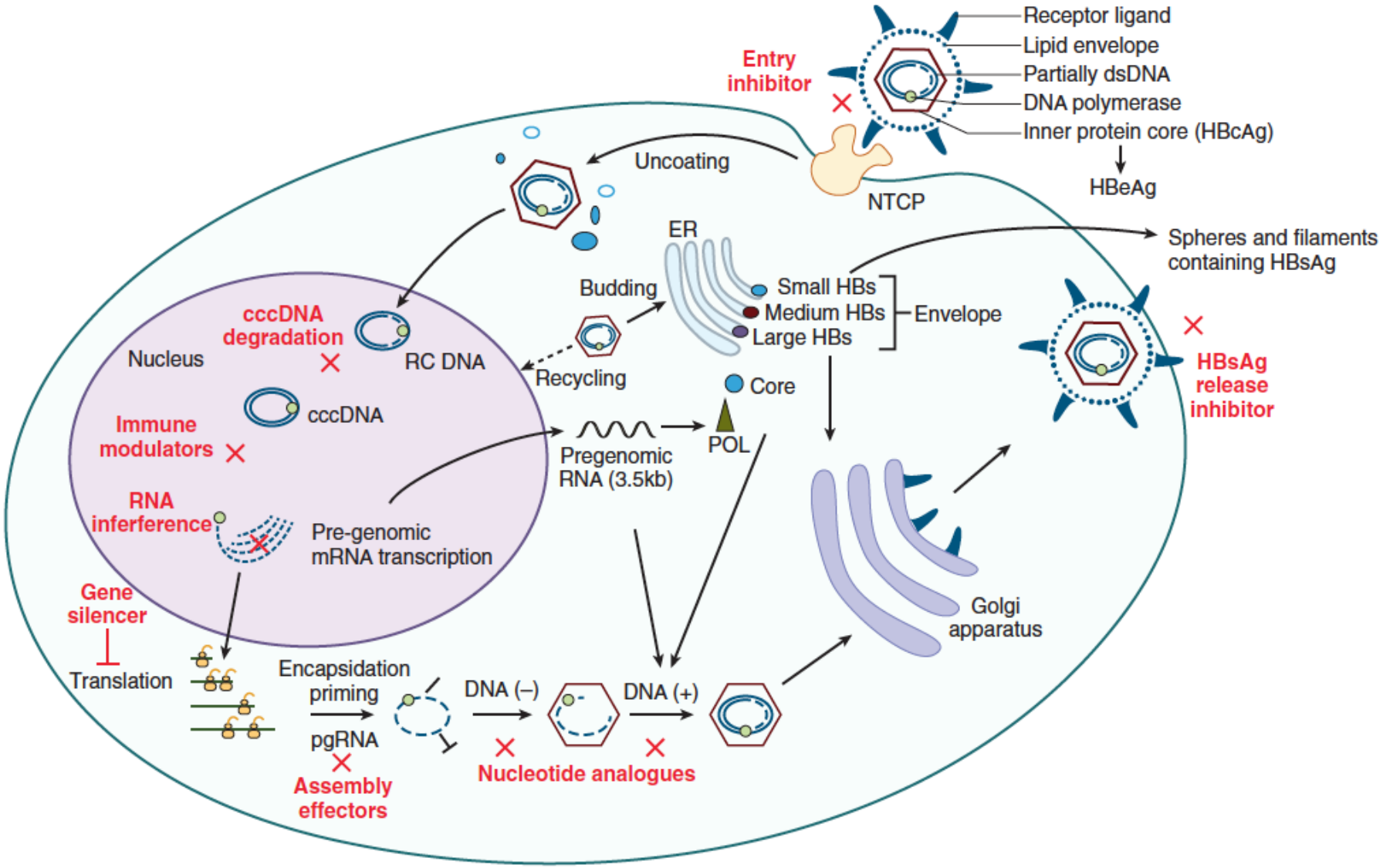
*Defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis;
†Defined by persistently normal ALT and high HBV DNA levels;
‡ Even if typical treatment indications are not fulfilled

EASL CPG HBV. J Hepatol 2017;67:370–98

HBV GUIDELINES AND GUIDANCE

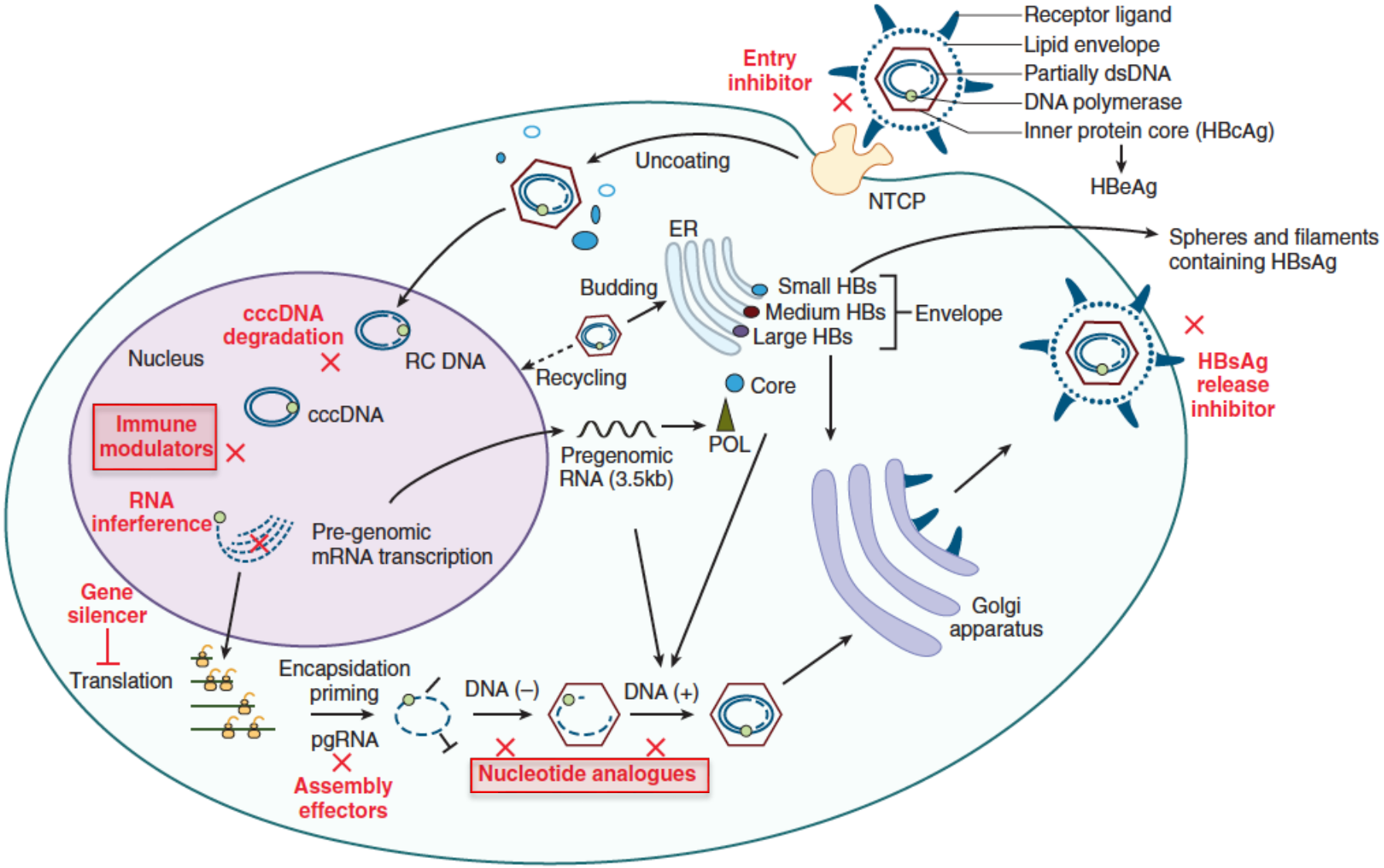
* Who needs to be treated and why?
* How to treat and when to stop?

HBV life cycle and therapeutic targets



Janssen H., Reijnders J., Sonneveld M. In Zakim and Boyer 's Hepatology, 2017

HBV life cycle and therapeutic targets



Janssen H., Reijnders J., Sonneveld M. In Zakim and Boyer 's Hepatology, 2017

First-Line Antiviral Therapies in Adults with Chronic Hepatitis B (Not Head-to-Head Comparisons)

HBeAg Positive	Peg-IFN*	Entecavir†	Tenofovir Disoproxil Fumarate†	Tenofovir Alafenamide‡
% HBV-DNA suppression (cutoff to define HBV-DNA suppression)§	30-42 (<2,000-40,000 IU/mL) 8-14 (<80 IU/mL)	61 (<50-60 IU/mL)	76 (<60 IU/mL)	73 (<29 IU/mL)
% HBeAg loss	32-36	22-25	—	22
% HBeAg seroconversion	29-36	21-22	21	18
% Normalization ALT	34-52	68-81	68	—
% HBsAg loss	2-7 11 (at 3 years posttreatment)	4-5	8	1

HBeAg Negative	Peg-IFN	Entecavir	Tenofovir Disoproxil Fumarate†	Tenofovir Alafenamide‡
% HBV-DNA suppression (cutoff to define HBV-DNA suppression)‖	43 (<4,000 IU/mL) 19 (<80 IU/mL)	90-91 (<50-60 IU/mL)	93 (<60 U/mL)	90 (<29 IU/mL)
% Normalization ALT¶	59	78-88	76	81
% HBsAg loss	4 6 (at 3 years posttreatment)	0-1	0	<1

References: [6-16].

*Assessed 6 months after completion of 12 months of therapy.

†Assessed after 3 years of continuous therapy.

‡Assessed after 2 years of continuous therapy.

§HBV DNA <2,000-40,000 IU/mL for peg-IFN; <60 IU/mL for entecavir and tenofovir disoproxil fumarate; <29 IU/mL for tenofovir alafenamide.

‖HBV DNA <20,000 IU/mL for peg-IFN; <60 IU/mL for entecavir and tenofovir disoproxil fumarate; <29 IU/mL for tenofovir alafenamide.

¶ALT normalization defined by laboratory normal rather than ≤35 and ≤25 U/L for males and females.

Terrault et al. HEPATOLOGY, Vol. 67, No. 4, 2018

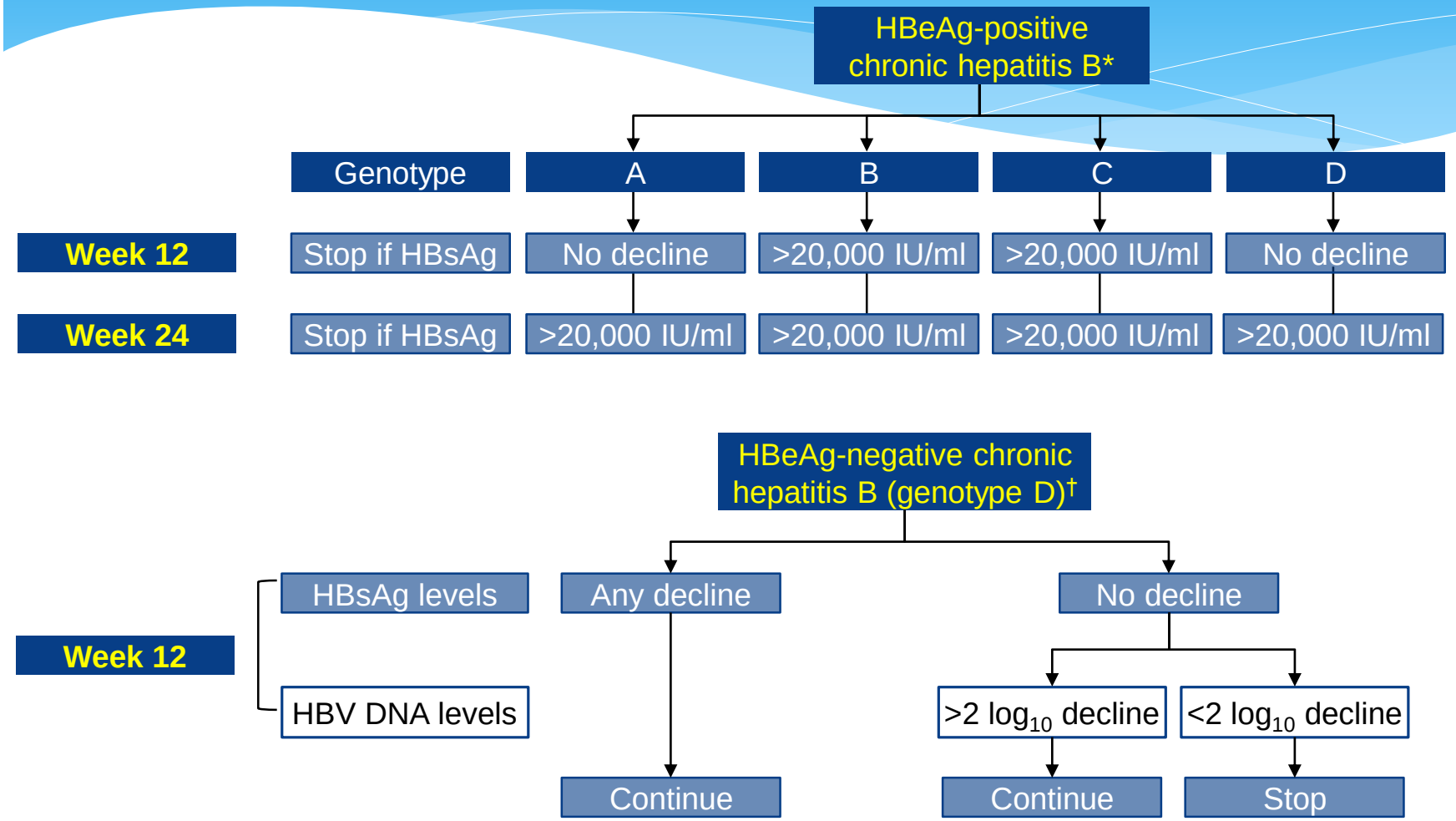
Baseline Predictors of Response to Treatment With Peg-IFN-α

HBeAg-Positive Patients	HBeAg-Negative Patients
Genotype A/B	Higher ALT
Higher ALT	Lower HBV DNA
Lower HBV DNA	Younger age
Older age	Female sex
Female sex	Lower HBsAg
Lower HBsAg	
Lower HBeAg	

Baseline parameters associated with higher response rates to 1 year of pegylated interferon-α therapy. Variables associated with response on a continuous scale are designated *higher* or *lower* if cutoff levels were not reported.

Janssen H., Reijnders J., Sonneveld M. In Zakim and Boyer 's Hepatology, 2017

Predictors of Peg-IFNα response and stopping rules



*Evidence level II-2, grade of recommendation 2; †Evidence level II-2, grade of recommendation 1

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Indications for selecting ETV or TAF over TDF*

* *In some circumstances ETV or TAF may be a more appropriate treatment choice than TDF*

Age	• >60 years
Bone disease	• Chronic steroid use or use of other medications that worsen bone density • History of fragility fracture • Osteoporosis
Renal alteration†	• eGFR <60 ml/min/1.73 m^2 • Albuminuria >30 mg/24 h or moderate dipstick proteinuria • Low phosphate (<2.5 mg/dl) • Haemodialysis

*TAF should be preferred to ETV in patients with previous exposure to NAs; †ETV dose needs to be adjusted if eGFR <50 ml/min; no dose adjustment of TAF is required in adults or adolescents (aged ≥12 years and ≥35 kg body weight) with estimated CrCl ≥15 ml/min or in patients with CrCl <15 ml/min who are receiving haemodialysis

EASL CPG HBV. J Hepatol 2017;67:370–98

EASL Recommendations for NAs cessation

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)*

EASL CPG HBV. J Hepatol 2017;67:370–98

Novel biomarkers to predict off-treatment response

* ***Viral markers to predict outcome after NAs cessation***
  - End of treatment qHBsAg level (cut-off have not yet been defined)
  - HBsAg kinetics during treatment
  - Quantification of serum Hepatitis B core-related antigen (HBcrAg) and/or of circulating viral RNAs appearing promising
  - Need for assay standardization and evaluation in clinical trials

Outcome after long-term NAs treatment cessation

End of treatment qHBsAg level as a guide for safe NAs cessation?

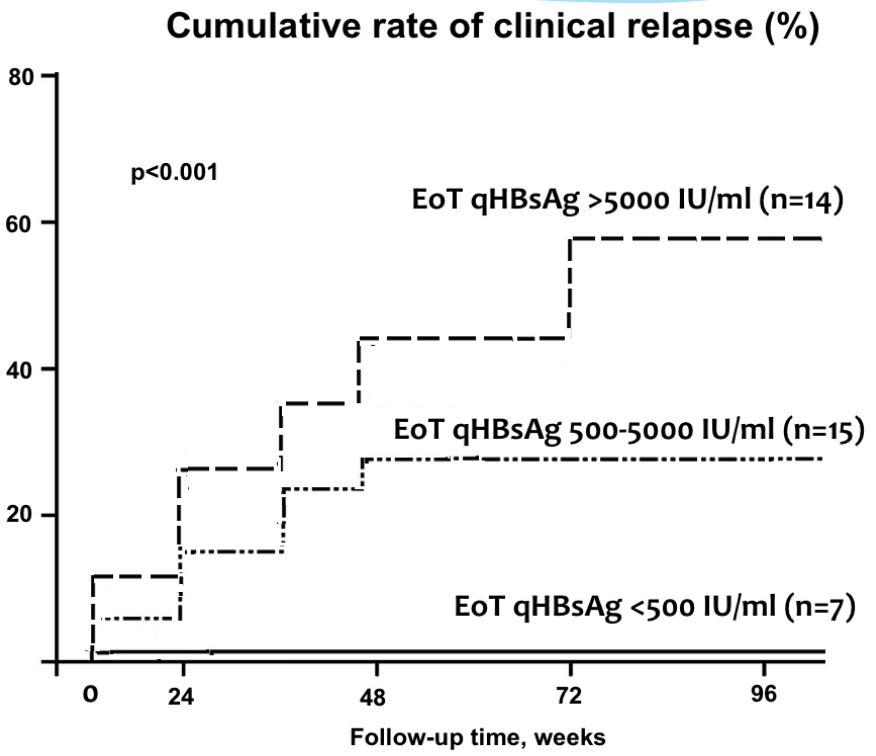
36 patients treated with NAs
(mean duration - 77.4±23.5 mo)
Before NAs therapy

- HBeAg-positive, n (%) - 5 (13.9%)
- HBV genotype D, n (%) - 21 (91.3%)

Type of NAs therapy, n (%)

- *ETV - 26 (72.2%)*
- *TDF - 4 (11.1%)*
- *TBV - 6 (16.7%)*

Off-treatment follow-up – 24 mo

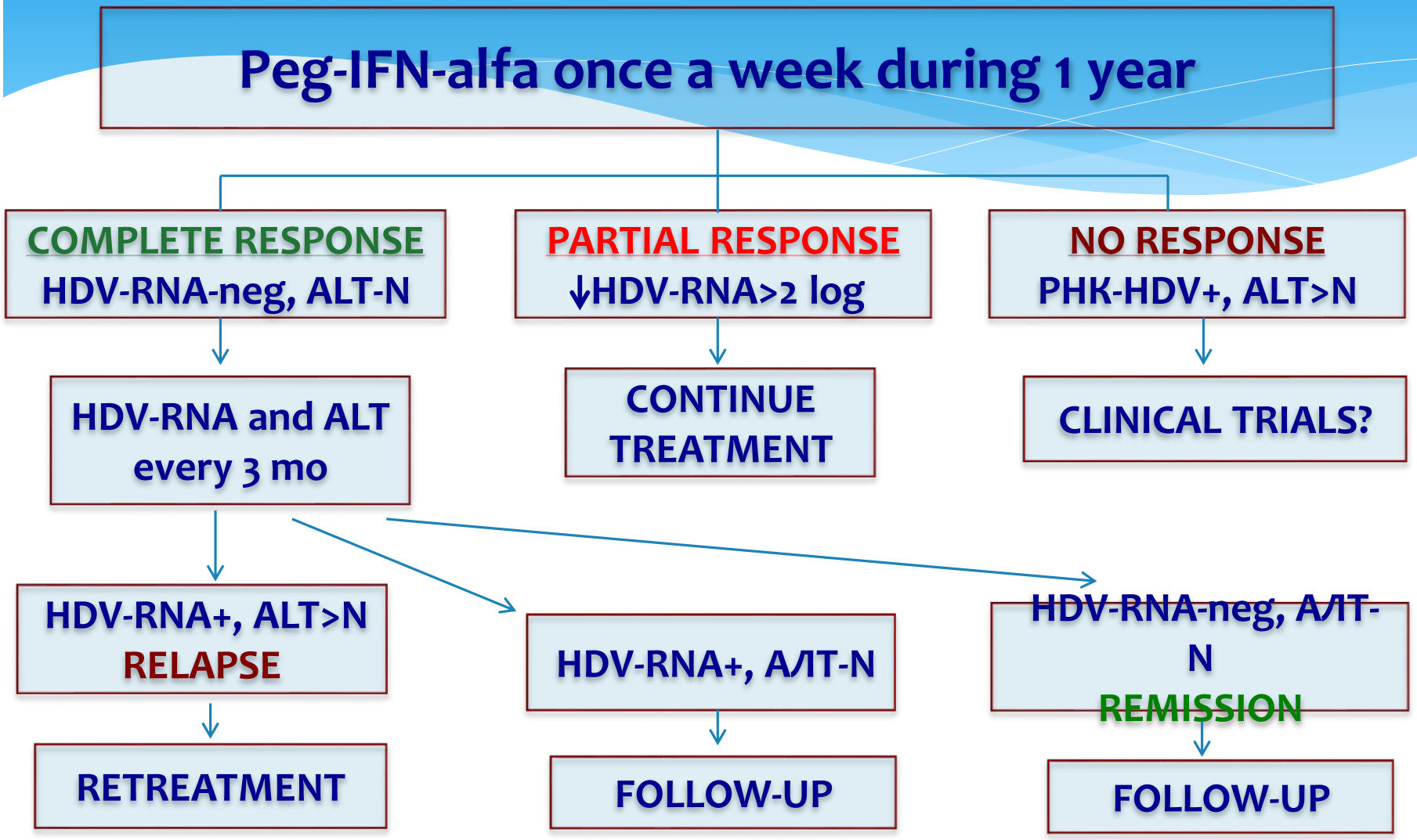


Abdurakhmanov D.T. et al. personal observation, 2018

HDV TREATMENT

* **CURRENT OPTIONS:**
  - *Peg-IFN-alfa (for 1 year) ± NAs (if HBV-DNA>2000 IU/ml);*
* **FUTURE OPTIONS:**
  - *Peg-IFN-λ*
  - *Nuclear Acid Polymers*
  - *Lonafarnib*
  - *Myrcludex-B*

HDV treatment with Peg-IFN-alfa



Yurdaydin C., 2008

HDV TREATMENT

* **CURRENT OPTIONS:**
  - *Peg-IFN-alfa (for 1 year) ± NAs (if HBV-DNA>2000 IU/ml);*
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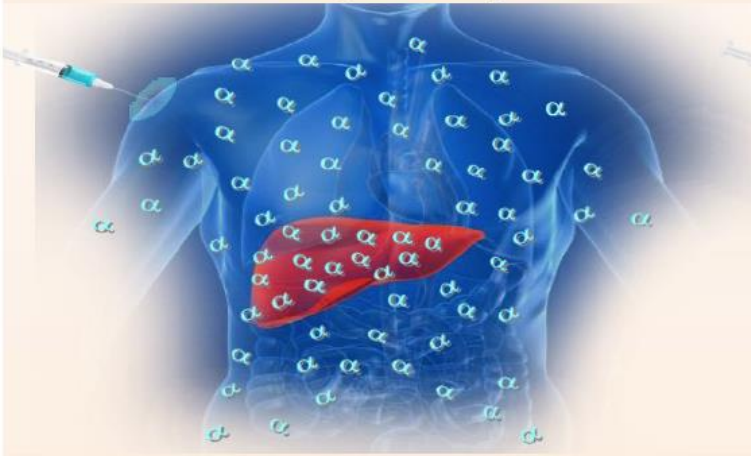
  - *Peg-IFN-λ*
  - *Nuclear Acid Polymers*
  - *Lonafarnib*
  - *Myrcludex-B*

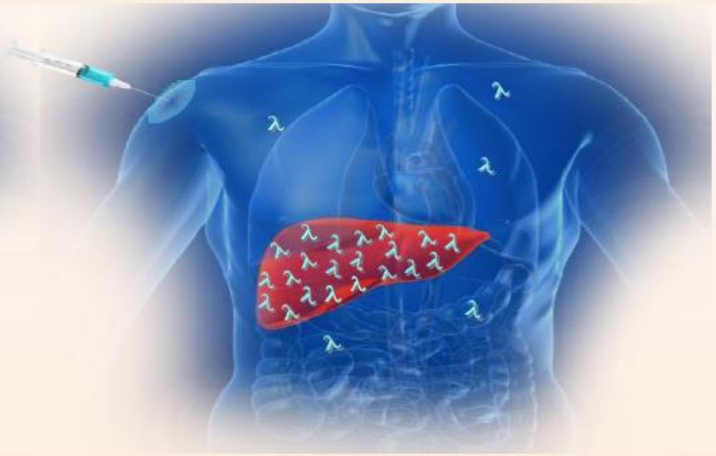
Peg-IFN-lambda in HDV

Potential Impact of Lambda Receptor Distribution

*IFN alfa receptors **widely** distributed throughout body.*



*Lambda receptors NOT **widely** distributed throughout body.*



*Potential for **MORE** IFN-associated abnormalities:*

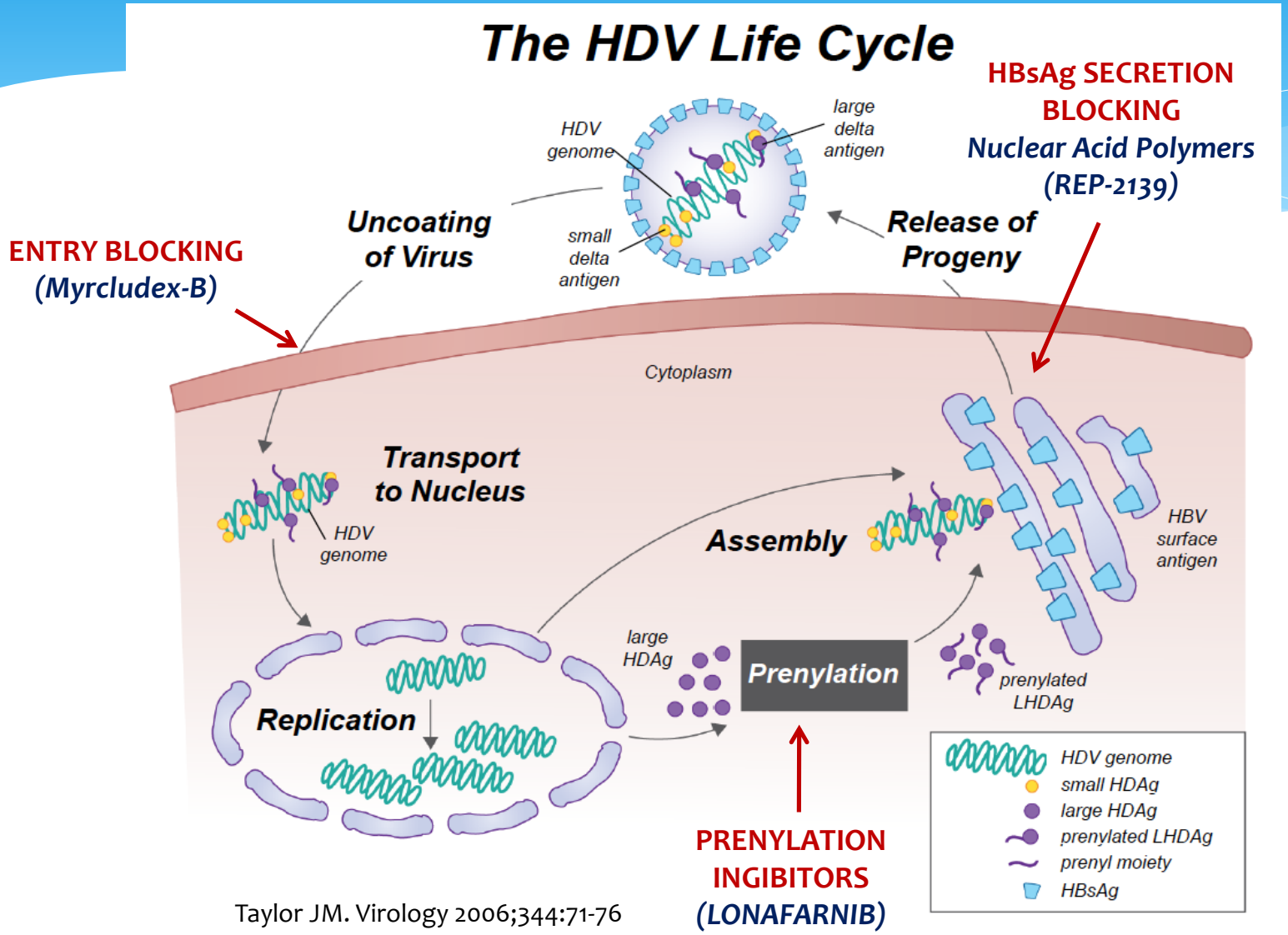
- ↑ *Neutropenia*
- ↑ *Thrombocytopenia*
- ↑ *Flu-like Symptoms*
- ↑ *Musculoskeletal Symptoms*

*Potential for **LESS** IFN-associated abnormalities:*

- ↓ *Neutropenia*
- ↓ *Thrombocytopenia*
- ↓ *Flu-like Symptoms*
- ↓ *Musculoskeletal Symptoms*

Donnelly R et al, J Interferon Cytokine Res, 2010, 30(8): 555.

HDV life cycle and treatment targets

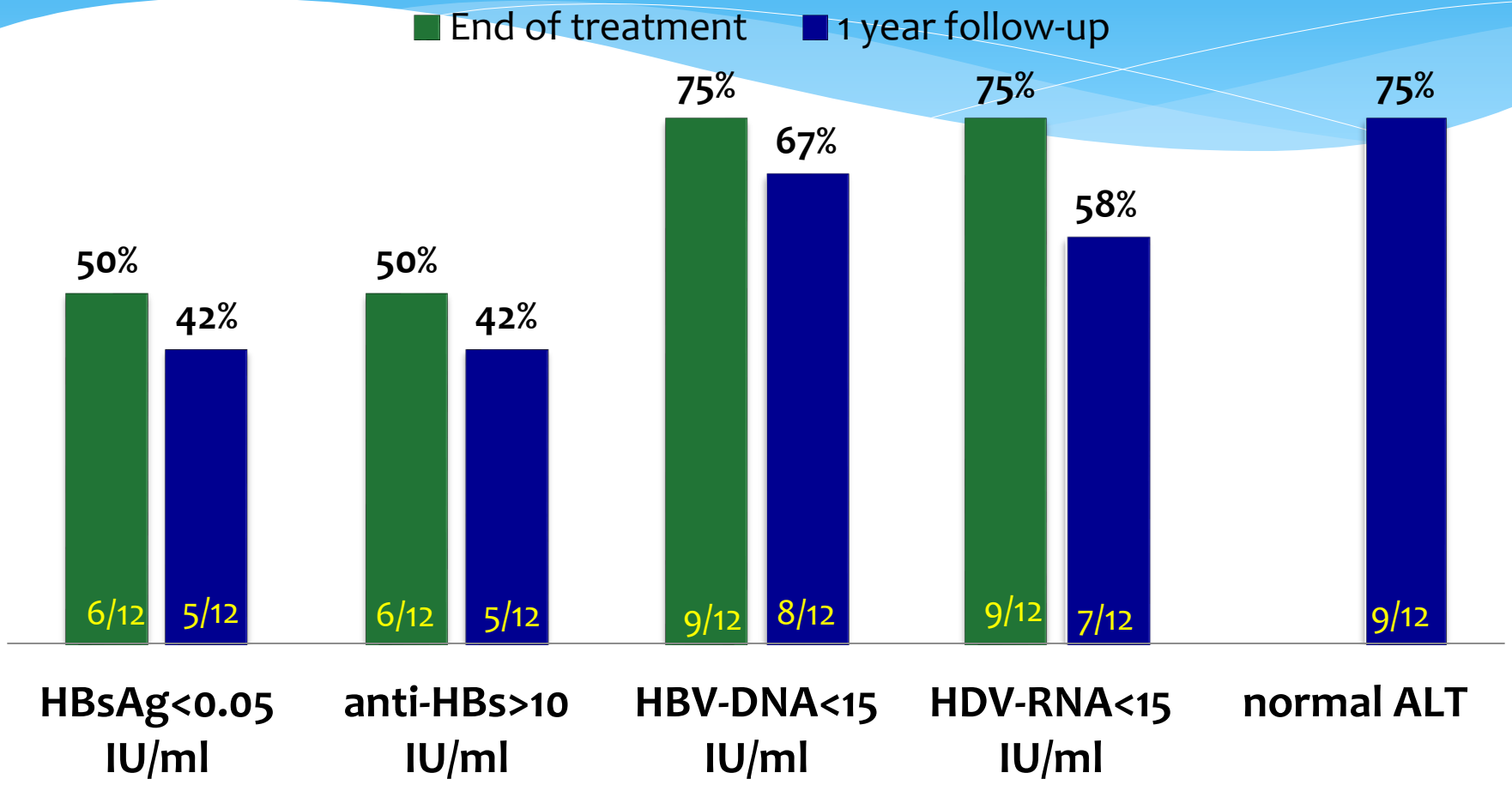


Taylor JM. Virology 2006;344:71-76

LONAFARNIB in HDV

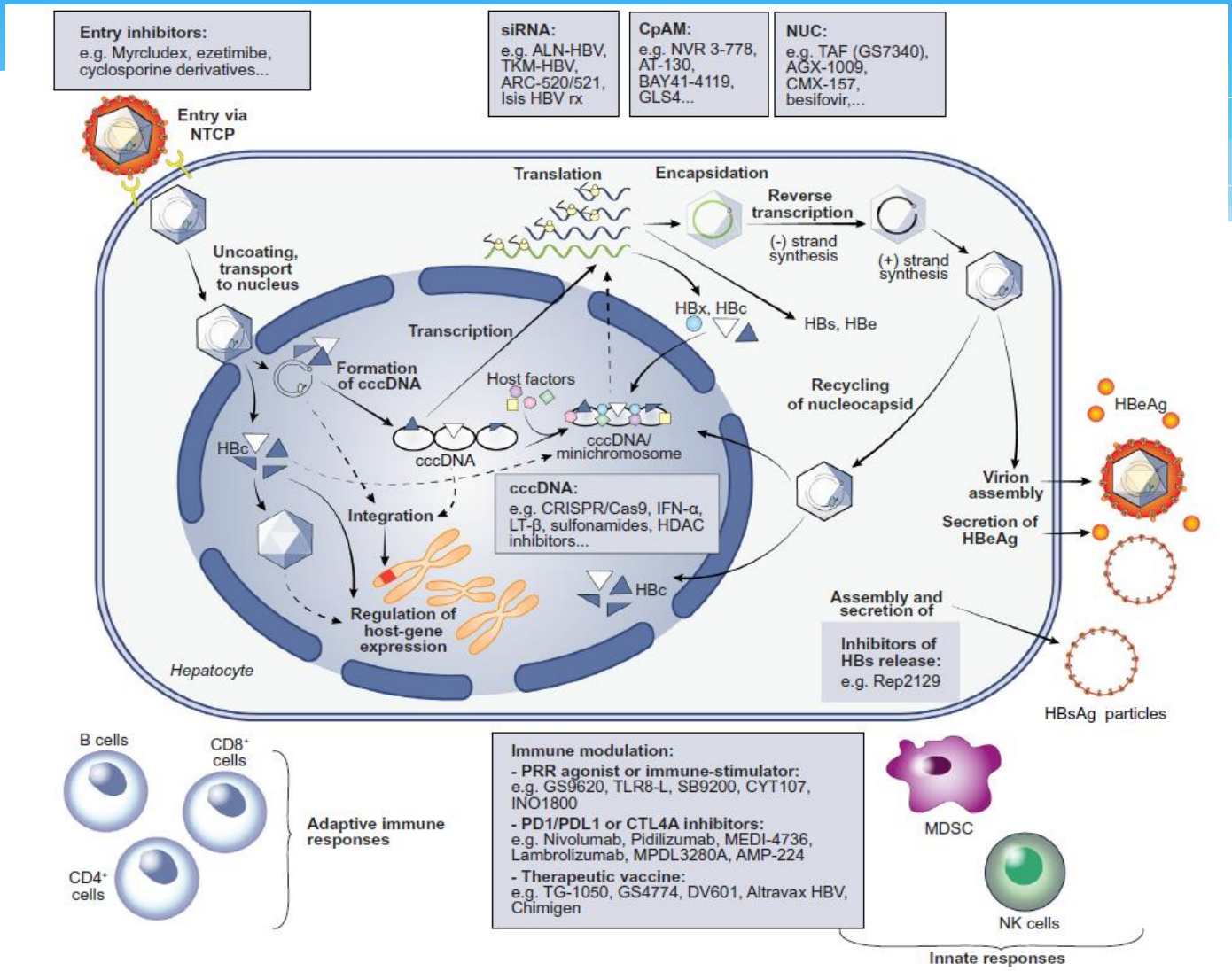
HDV Registration Options	Clinical Description	Treatment Option All Oral	Treatment Option Triple Combo	Treatment Option Mono
Cure	HDV RNA Negativity + ALT Normalization	Lonafarnib + Ritonavir	Lonafarnib + Ritonavir + Lambda	Lambda
Chronic Treatment	HDV RNA Reduction + ALT Normalization	Lonafarnib + Ritonavir		

REP-2139+Peg-IFN-alfa in HDV (12 non-cirrhotic pts)



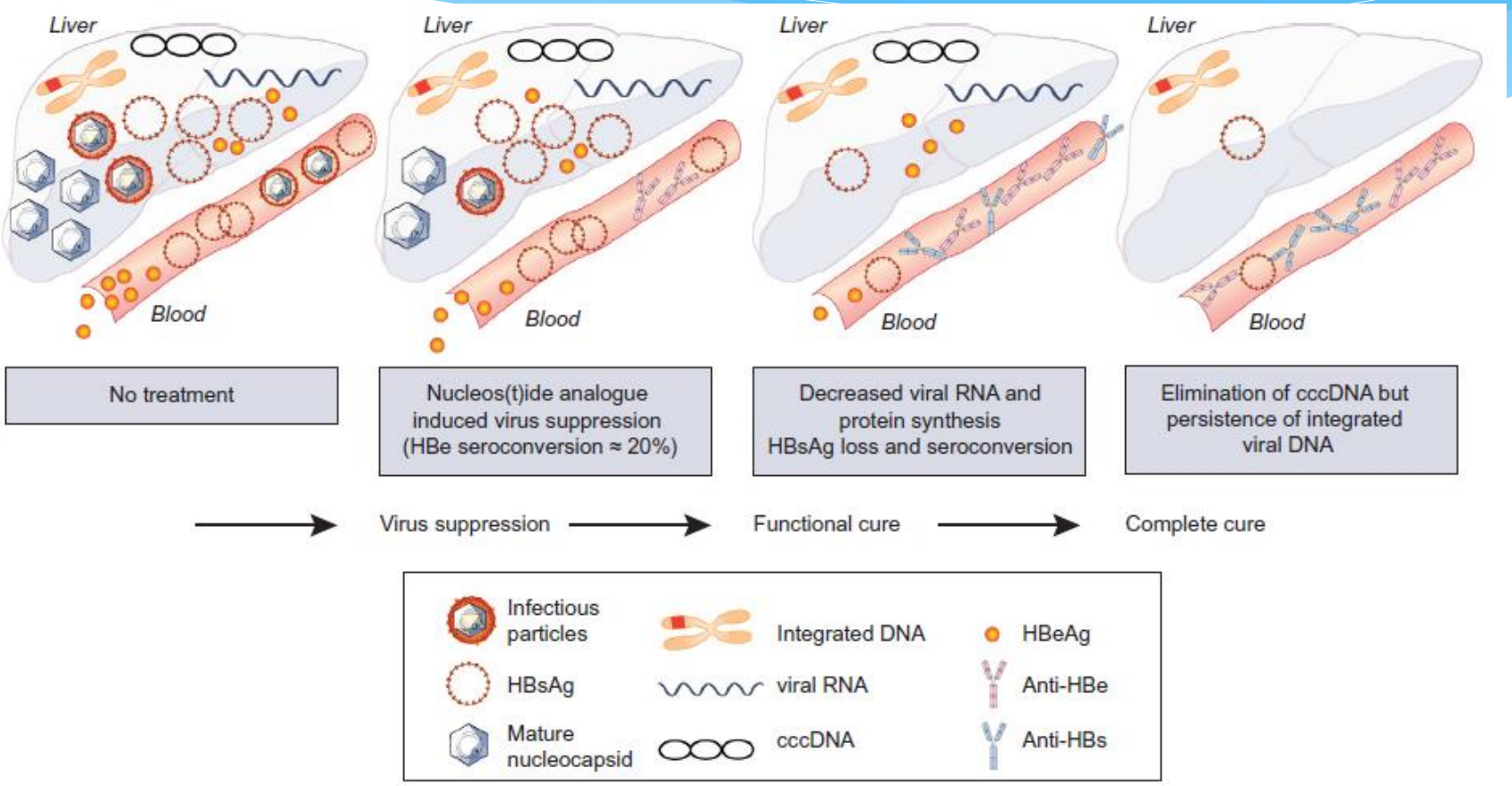
Bazinet M., Pantea V., Vaillant A. et al., Lancet Gastr. Hepat., 2017

HBV life cycle and main classes of antivirals in development



Durantel D, Zoulim F. J Hepatol 2016;64:S117–31

Schematical representation of various types of “cure”



Durantel D, Zoulim F. J Hepatol 2016;64:S117–31

Unresolved issues and unmet needs

* When to start antiviral therapy in patients with HBeAg-positive chronic HBV infection
* Stopping rules for HBeAg-negative patients treated with an NA
* Retreatment criteria after NA discontinuation
* How to accelerate HBsAg decline in long-term NA-treated patients
* Better baseline or on-treatment predictors of sustained response in patients treated with PegIFNα
* Definition of the residual risk of HCC in patients on long-term NA therapy and impact on surveillance
* Requirement for new treatments with finite duration and high cure rates
* Novel endpoints to define a cure of HBV infection

EASL CPG HBV. J Hepatol 2017;67:370–98