Challenge virologique du traitement du VHB

Dr Laurence Bocket

JRPI 11/10/2022

service de VIROLOGIE
CHRU de Lille

Centre Hospitalier Régional Universitaire de Lille

Liens d’intérêt

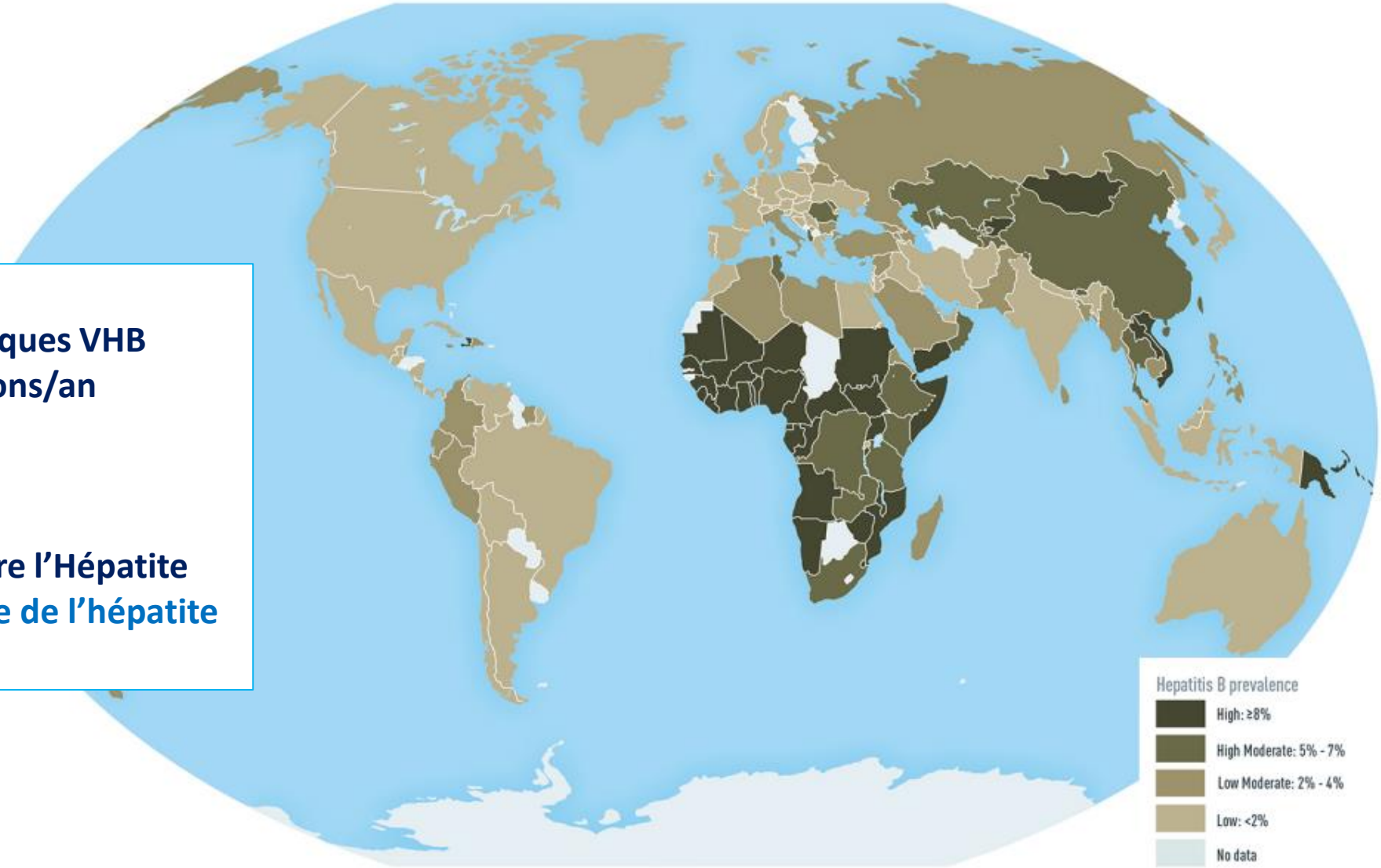
honoraires d’orateur
participation aux frais de formation continue/congrès et aide financière aux études viro-cliniques

laboratoires pharmaceutiques
Gilead Sciences; MSD; ViiV Healthcare

OMS Juillet 2022:

- **296 millions porteurs chroniques VHB**
- **1,5 million nouvelles infections/an**
- **820000 décès/an**

→ journée mondiale OMS contre l'Hépatite 2022 « rendre la prise en charge de l'hépatite plus accessible »



MAP 4-4. **Prevalence of hepatitis B virus infection**[1]

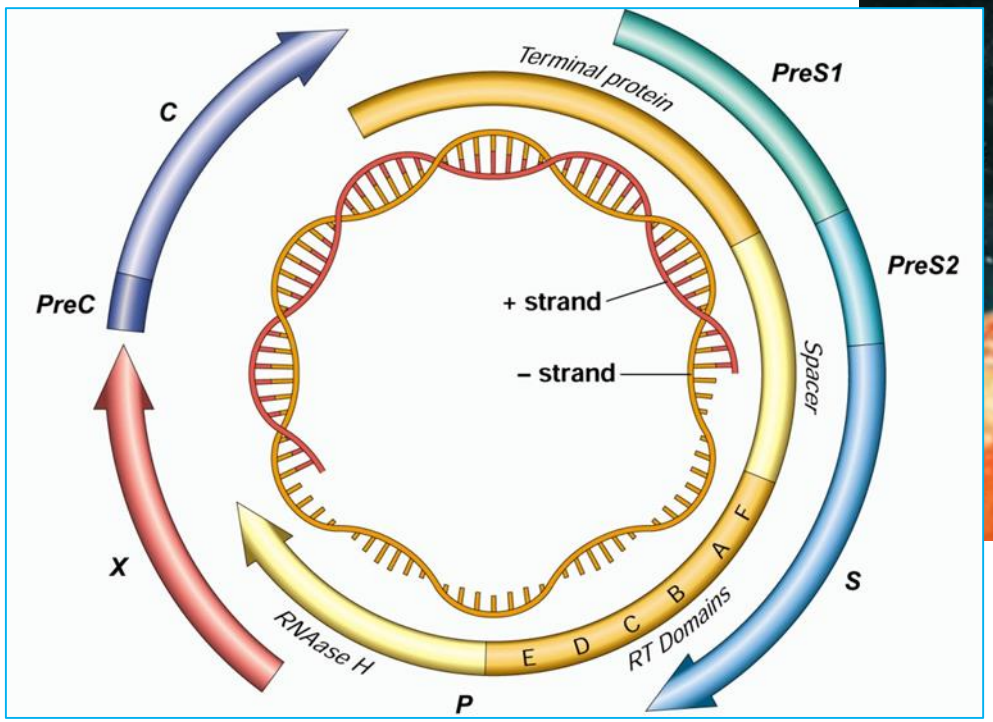
Boundary representation is not necessarily authoritative.

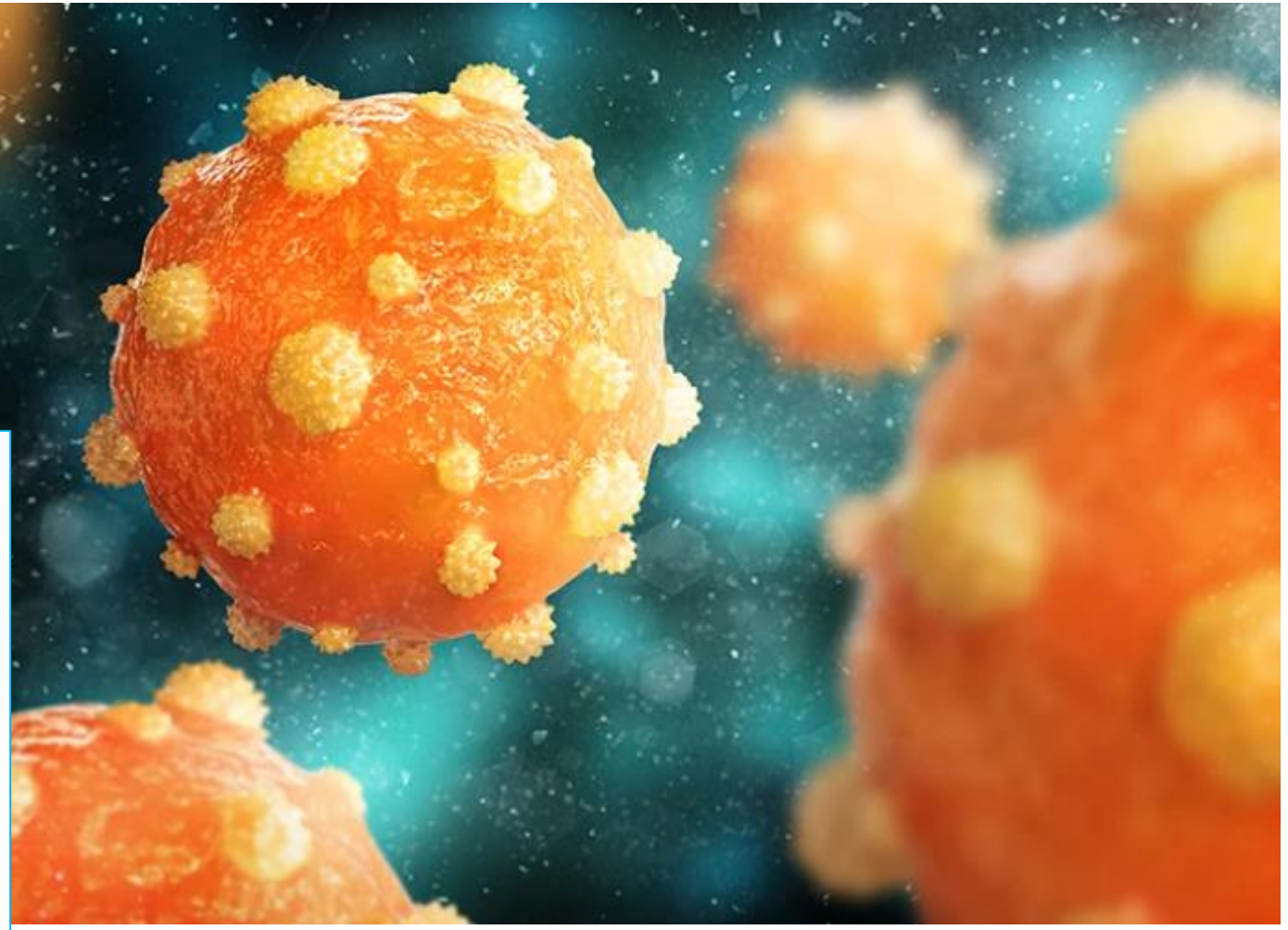
[1] Disease data source: Schweitzer A, Horn J, Mikolajczyk R, Krause G, Ott J. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. www.thelancet.com. 2015.Vol 386.

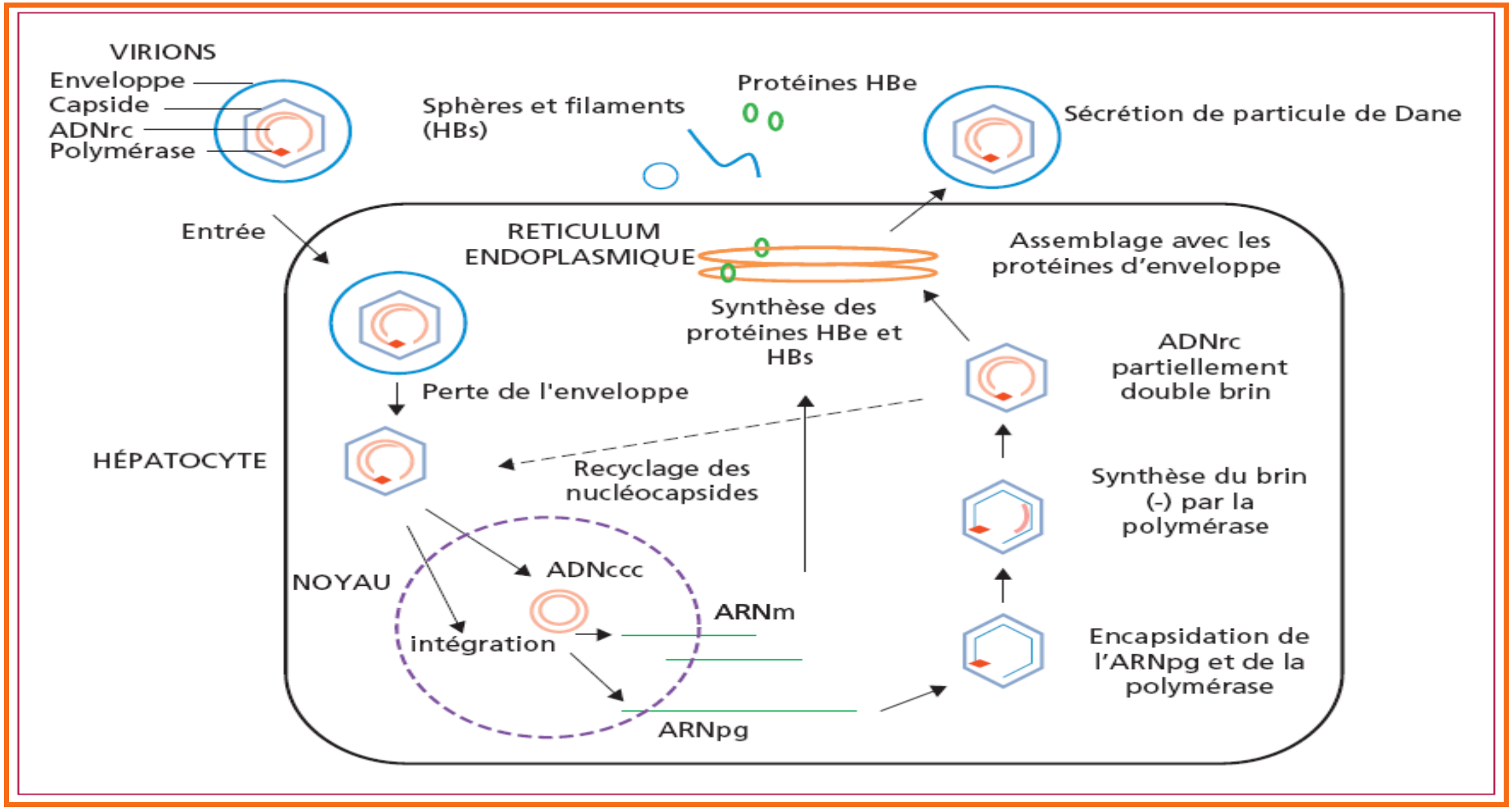
Source: Centers for Disease Control and Prevention. CDC Yellow Book 2020: Health Information for International Travel. New York: Oxford University Press; 2019.

Hepadnaviridae, hepadnavirus

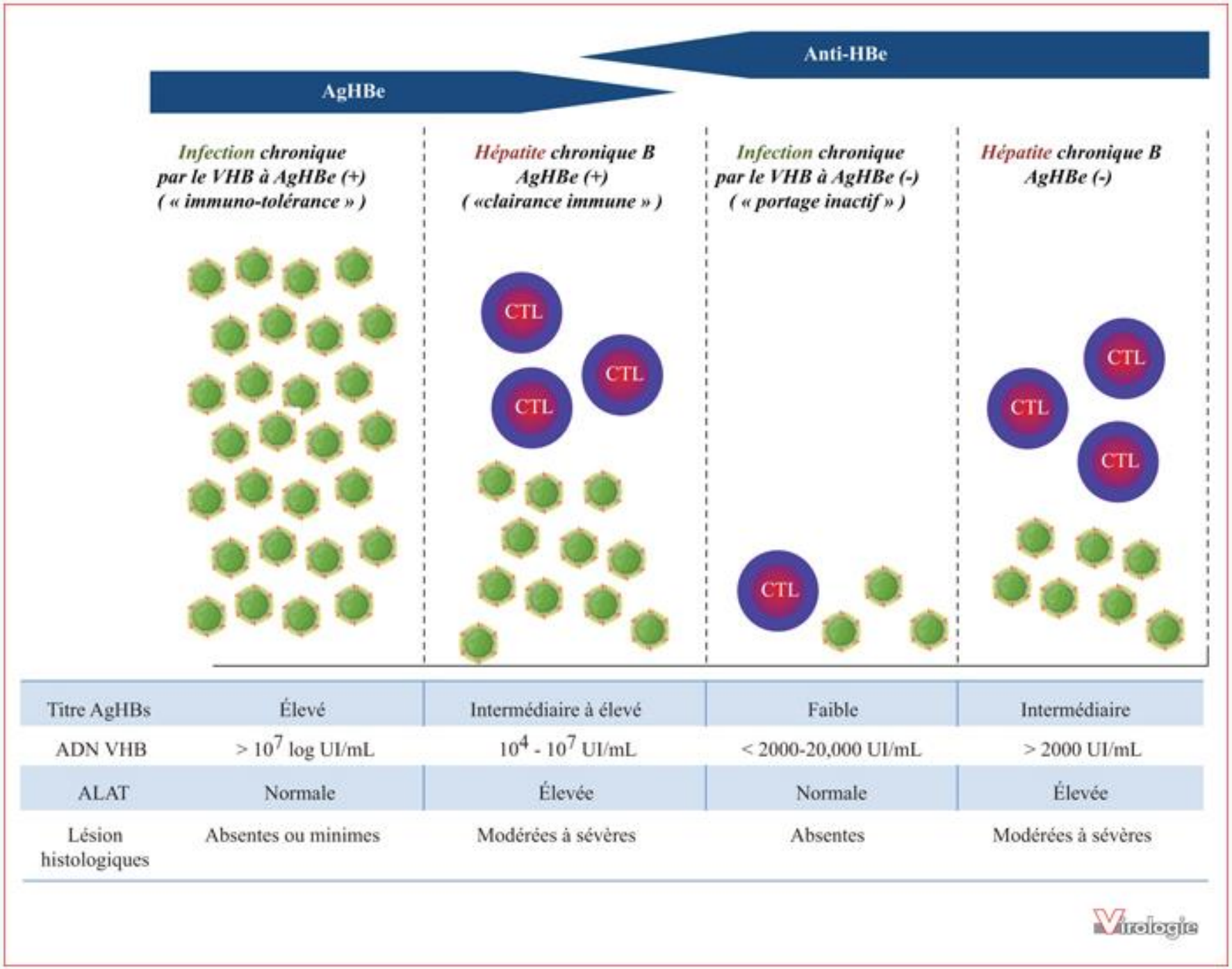
- Virus enveloppé → Ag HBs
- Génome ADN
- Tropisme hépatique
- Spécifique d'espèce





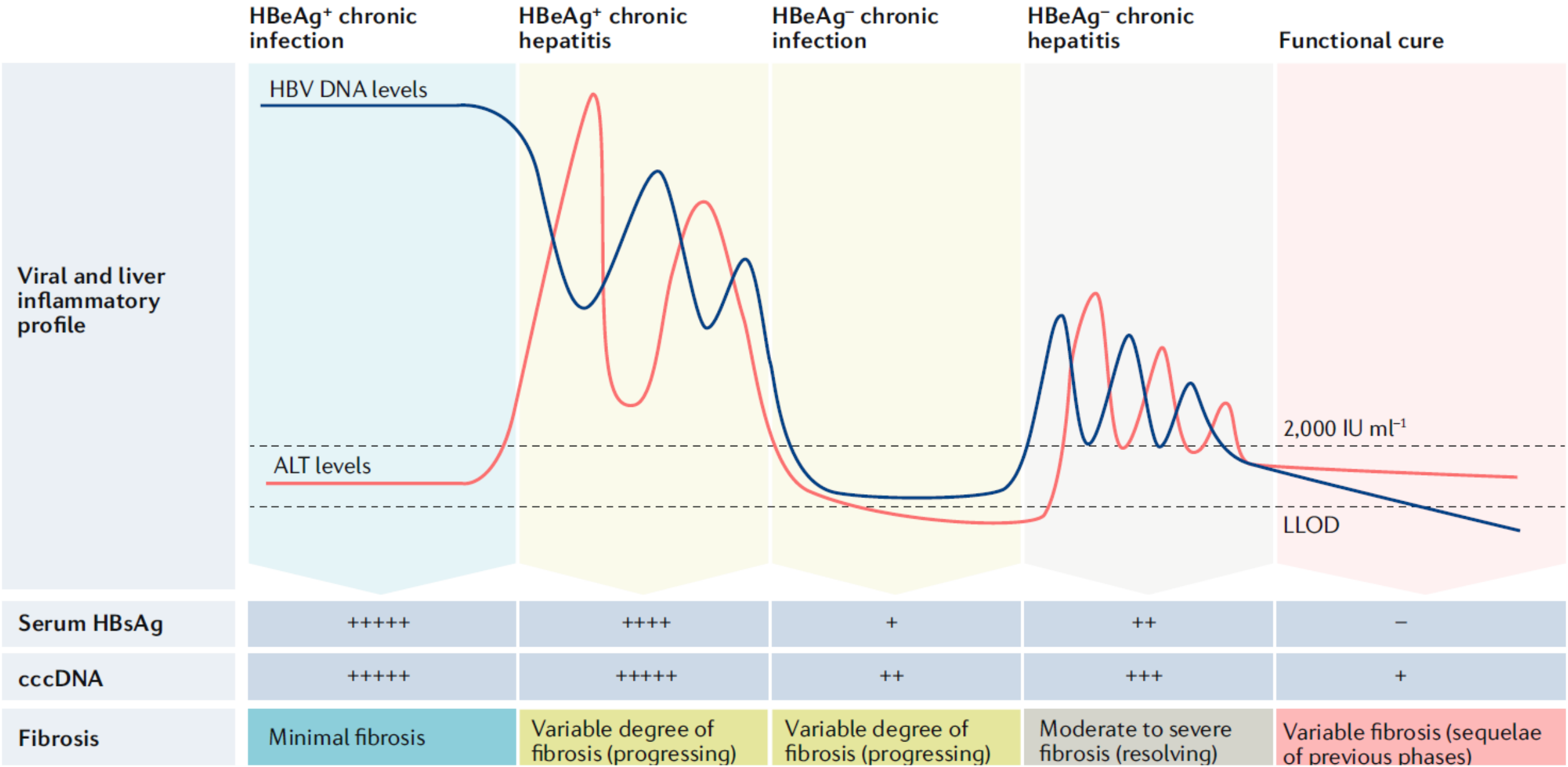

VIRIONS
Enveloppe
Capside
ADNrc
Polymérase
Sphères et filaments (HBs)
Protéines HBe
Sécrétion de particule de Dane
Entrée
RETICULUM ENDOPLASMIQUE
Assemblage avec les protéines d'enveloppe
Synthèse des protéines HBe et HBs
ADNrc partiellement double brin
Perte de l'enveloppe
HÉPATOCYTE
Recyclage des nucléocapsides
Synthèse du brin (-) par la polymérase
NOYAU
ADNccc
ARNm
intégration
Encapsidation de l'ARNpg et de la polymérase
ARNpg

Histoire naturelle infection VHB



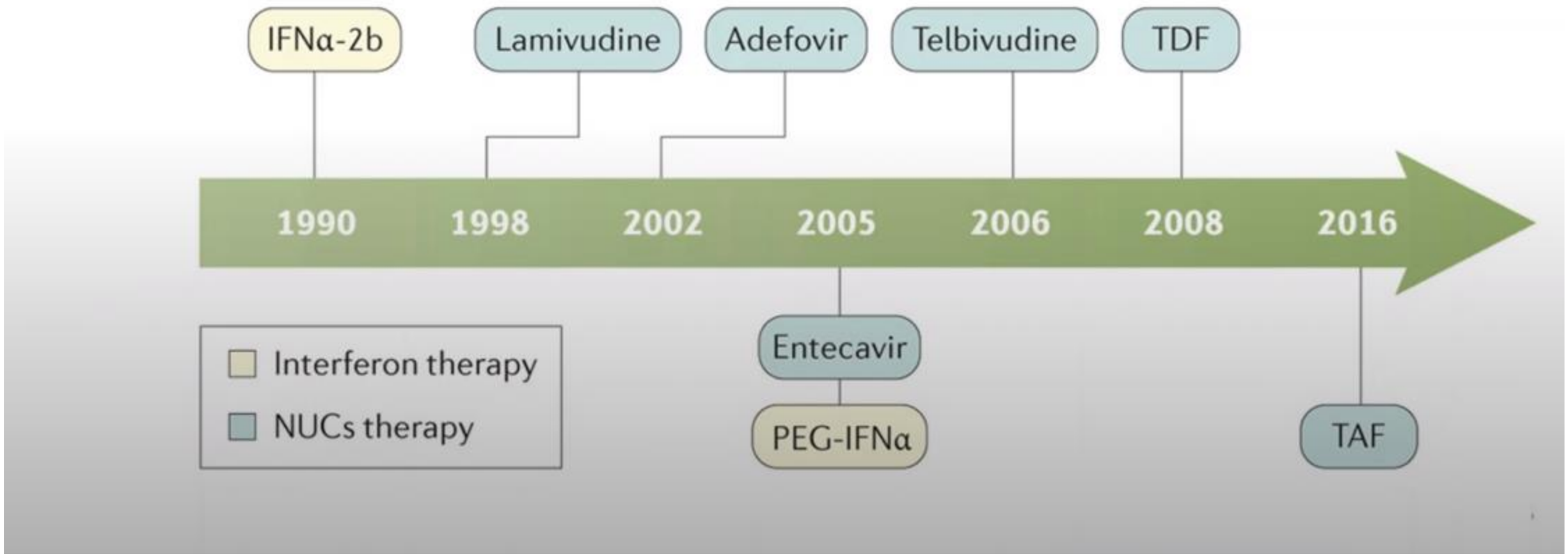
Titre AgHBs	Élevé	Intermédiaire à élevé	Faible	Intermédiaire
ADN VHB	> 10^7 log UI/mL	10^4 - 10^7 UI/mL	< 2000-20,000 UI/mL	> 2000 UI/mL
ALAT	Normale	Élevée	Normale	Élevée
Lésion histologiques	Absentes ou minimes	Modérées à sévères	Absentes	Modérées à sévères

Virologie



Fanning GC, et al. Nature Review 2019

Currently approved therapeutics for hepatitis B



Yuen MF et al, Nat Rev Dis Primers 2018

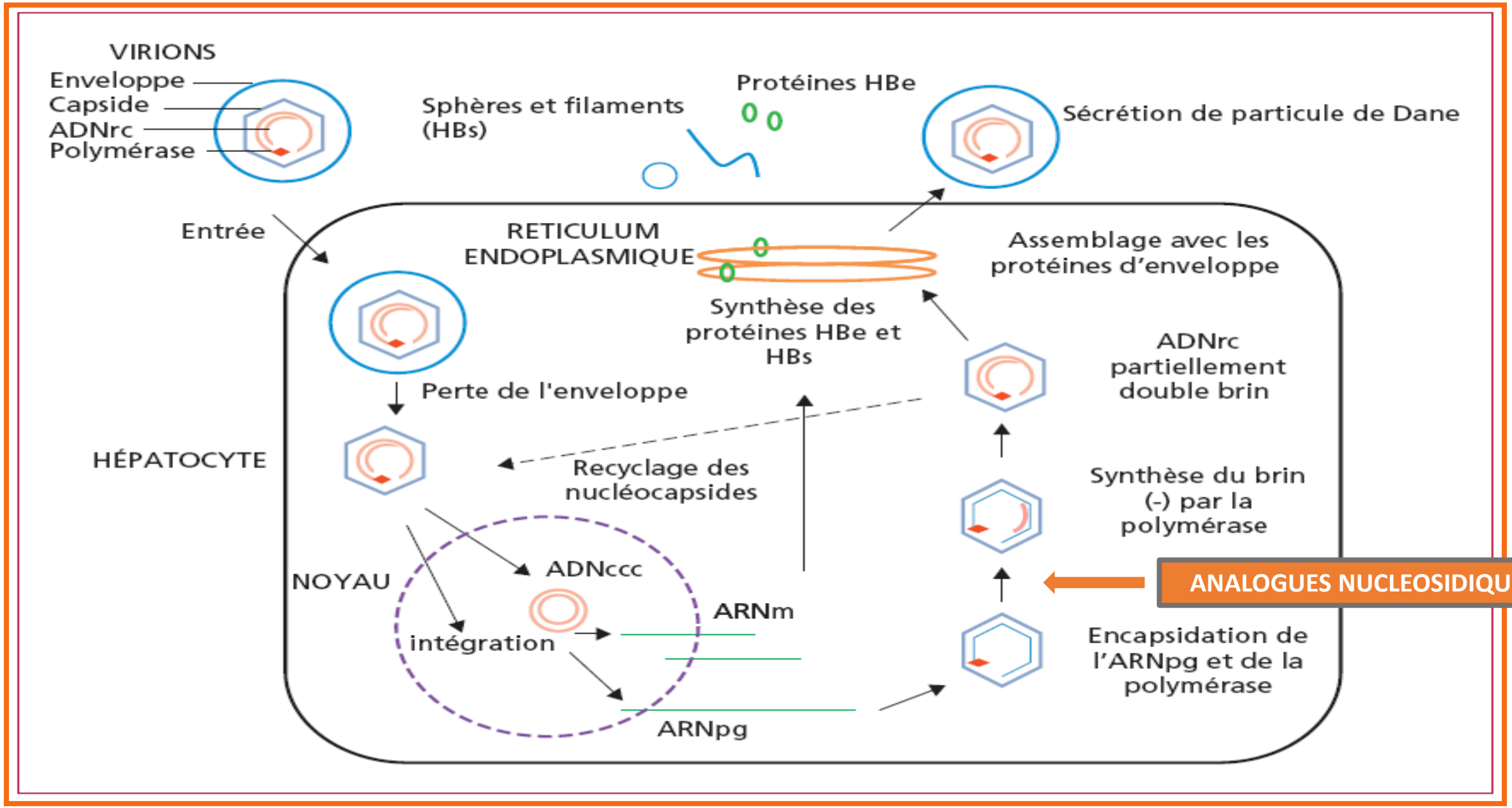

VIRIONS
Enveloppe
Capside
ADNrc
Polymérase
Sphères et filaments (HBs)
Protéines HBe
Sécrétion de particule de Dane
Entrée
RETICULUM ENDOPLASMIQUE
Assemblage avec les protéines d'enveloppe
Synthèse des protéines HBe et HBs
ADNrc partiellement double brin
Perte de l'enveloppe
HÉPATOCYTE
Recyclage des nucléocapsides
Synthèse du brin (-) par la polymérase
NOYAU
ADNccc
ARNm
intégration
ANALOGUES NUCLEOSIDIQUES
Encapsidation de l'ARNpg et de la polymérase
ARNpg

Table 3. Results of main studies for the treatment of HBeAg-positive chronic hepatitis B at 6 months following 48 or 52 weeks of pegylated interferon alfa (PegIFNα) and at 48 or 52 weeks of nucleos(t)ide analogue therapy.

	PegIFN		Nucleoside analogues			Nucleotide analogues		
	PegIFNα2a	PegIFNα2b	LAM	TBV	ETV	ADV	TDF	TAF
Dose*	180 μg	100 μg	100 mg	600 mg	0.5 mg	10 mg	245 mg	25 mg
Anti-HBe-seroconversion	32%	29%	16–18%	22%	21%	12–18%	21%	10%
HBV DNA <60–80 IU/ml	14%	7%	36–44%	60%	67%	13–21%	76%	64%
ALT normalisation#	41%	32%	41–72%	77%	68%	48–54%	68%	72%
HBsAg loss	3%	7%	0–1%	0.5%	2%	0%	3%	1%

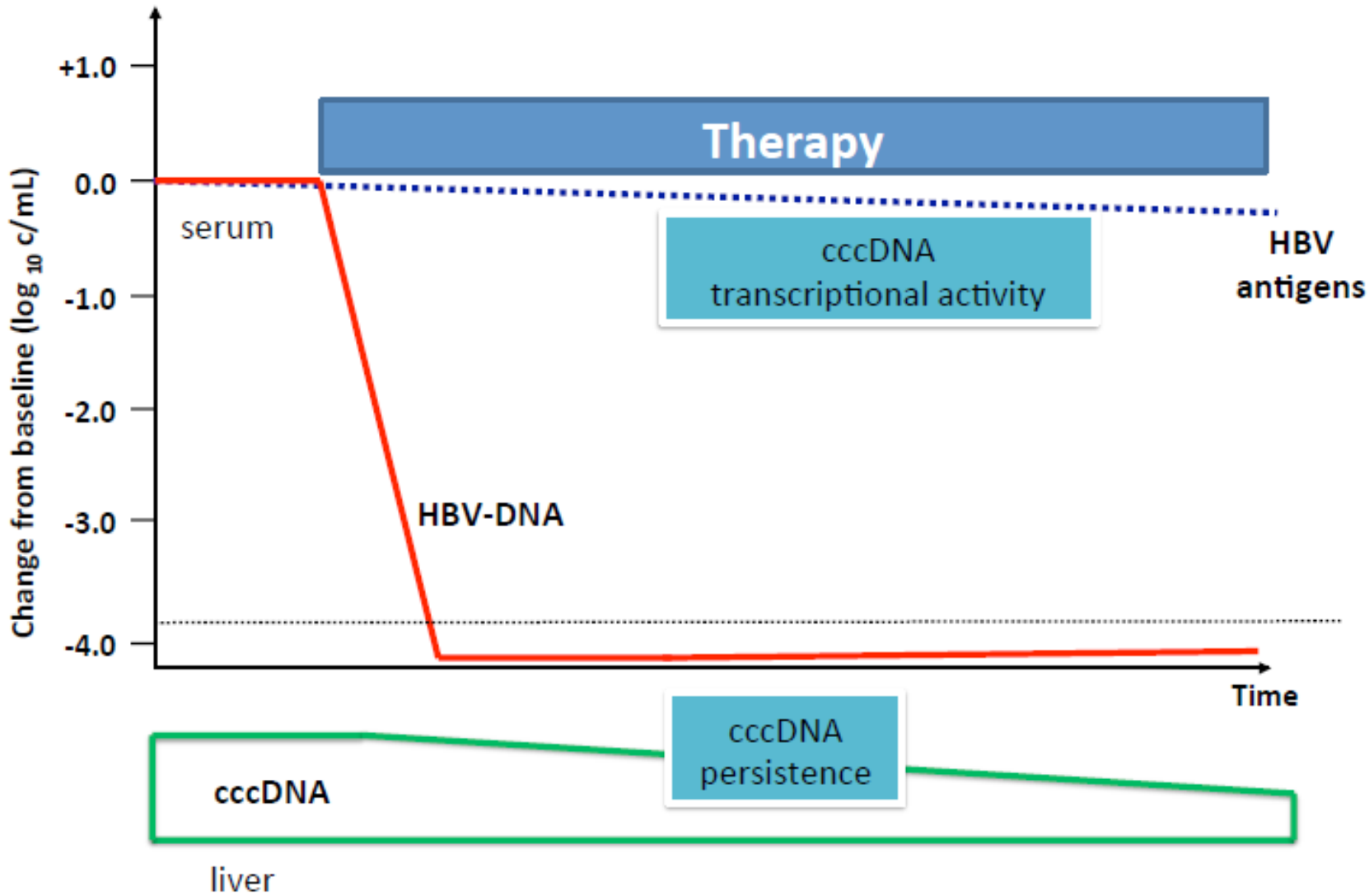
References: see EASL CPG 2012[1] for all drugs except for TAF.[76]
PegIFNα, pegylated interferon alfa; ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; LAM, lamivudine; TBV, telbivudine; ADV, adefovir; ALT, alanine aminotransferase.
* PegIFNα were given as percutaneous injections once weekly and nucleos(t)ide analogues as oral tablets once daily.
# The definition of ALT normalisation varied among different trials (*i.e.*, decrease of ALT to ⩽1.25-times the upper limit of normal (xULN) in the ETV or ⩽1.3×ULN in the TBV trial). The lower quantification limit of HBV DNA assays was different across studies: <29 IU/ml for TAF studies.

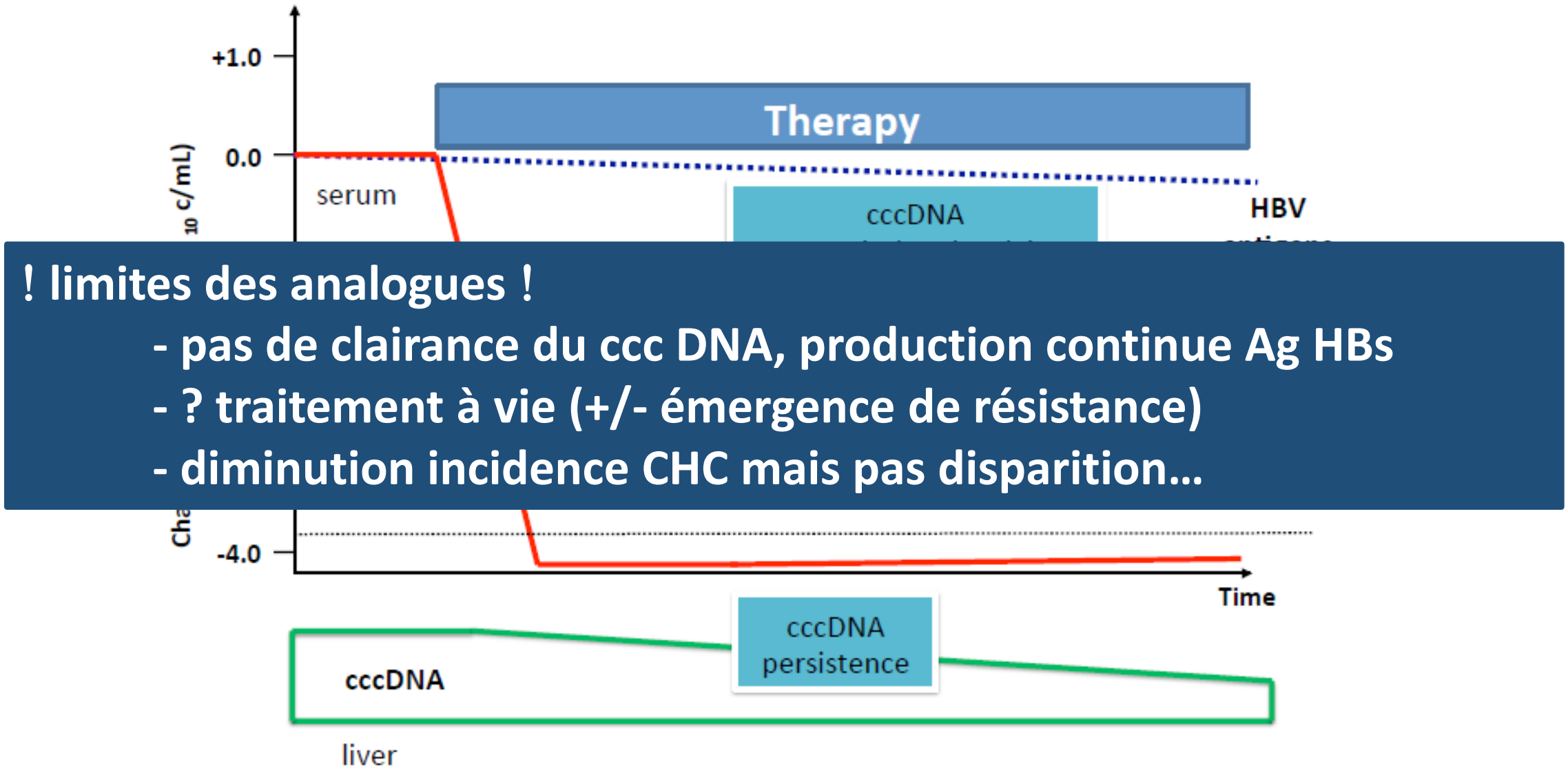
Table 4. Results of main studies for the treatment of HBeAg-negative chronic hepatitis B at 6 months following 48 weeks of pegylated interferon alfa (PegIFNα) and at 48 or 52 weeks of nucleos(t)ide analogue therapy.

	PegIFN	Nucleoside analogues			Nucleotide analogues		
	PegIFNα2a	LAM	TBV	ETV	ADV	TDF	TAF
Dose*	180 μg	100 mg	600 mg	0.5 mg	10 mg	245 mg	25 mg
HBV DNA <60–80 IU/ml	19%	72–73%	88%	90%	51–63%	93%	94%
ALT normalisation#	59%	71–79%	74%	78%	72–77%	76%	83%
HBsAg loss	4%	0%	0%	0%	0%	0%	0%

References: EASL CPG 2012[1] for all drugs except for TAF.[74]
PegIFNα, pegylated interferon alfa; ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; LAM, lamivudine; TBV, telbivudine; ADV, adefovir; ALT, alanine aminotransferase.
* PegIFNα was given as percutaneous injections once weekly and nucleos(t)ide analogues as oral tablets once daily.
# The definition of ALT normalisation varied among different trials (*i.e.*, decrease of ALT to ⩽1.25-times the upper limit of normal [ULN] in the ETV or ⩽1.3-times the ULN in the TBV trial). The lower quantification limit of HBV DNA assays was different across studies: for TAF studies it was <29 IU/ml.

Recos EASL 2017


+1.0
0.0
-1.0
-2.0
-3.0
-4.0
Change from baseline (log 10 c/mL)
Therapy
serum
cccDNA
transcriptional activity
HBV
antigens
HBV-DNA
Time
cccDNA
persistence
cccDNA
liver



! limites des analogues !

- pas de clairance du ccc DNA, production continue Ag HBs
- ? traitement à vie (+/- émergence de résistance)
- diminution incidence CHC mais pas disparition…

? Arrêter les NUCs ?

NA discontinuation
Recommendations

- NAs should be discontinued after confirmed HBsAg loss, with or without anti-HBs seroconversion (Evidence level II-2, grade of recommendation 1).
- 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).
- Discontinuation of NAs in selected non-cirrhotic HBeAg-negative patients who have achieved long-term ($\geqslant$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).

Recos EASL 2017, J.Hepatol 2017

Review

Current Trend in Antiviral Therapy for Chronic Hepatitis B

Rong-Nan Chien * and Yun-Fan Liaw *

Viruses **2022**, *14*, 434. https://doi.org/10.3390/v14020434

Table 1. Comparison of HBsAg loss between finite and indefinite long-term NUC therapy.

Source [Reference]	(Country/Year)	No. of Patient	NUC Therapy	HBsAg Loss	Annular HBsAg Loss Rate
Finite Therapy					
Chan H.L., et al. [53]	(Hong Kong/2011)	53	LAM 3 Yr	23%/5 Yr	4.6%
Hadziyannis S.J., et al. [49]	(Greece/2012)	33	ADV 4–5 Yr	39%/5 Yr	7.8%
Chi H., et al. [54]	(Canada/2015)	59	NUC 5 Yr	14%/3 Yr	4.7%
Honer Zu Siederdissen C., et al. [50]	(Germany/2016)	15	NUC > 3 Yr	20%/4 Yr	5.0%
Berg T., et al. [51]	(Germany/2017)	21	TDF > 4 Yr	19%/3 Yr	6.3%
Papatheodoridis G.V., et al. [52]	(Greece/ 2018)	57	ETV/TDF 5 Yr	16%/1 Yr	16%
Jeng W.J., et al. [48]	(Taiwan/2018)	383 (CHB)	ETV/TDF 3 Yr	16%/6 Yr	2.7%
		308 (LC)		9%/6 Yr	1.5%
Chen C.H., et al. [55]	(Taiwan/2019)	234	ETV 3 Yr	13%/5 Yr	2.6%
Indefinite long-term therapy					
Chen C.H., et al. [55]	(Taiwan/2019)	226	ETV 7 Yr	1.8%/7 Yr	0.25%
Hsu Y.C., et al. [40]	(Multination/2021)	4769	ETV/TDF 5.2Yr	2%/10 Yr	0.22%

NUC: nucleos(t)ige analogue; LAM: Lamivudine; ADV: Adefovir; TDF: Tenofovir disoproxil fumarate; ETV: Entecavir; TAF: Tenofovir alafenamide; Yr: Years.

Review

Current Trend in Antiviral Therapy for Chronic Hepatitis B

Rong-Nan Chien * and Yun-Fan Liaw *

Viruses 2022, *14*, 434. https://doi.org/10.3390/v14020434

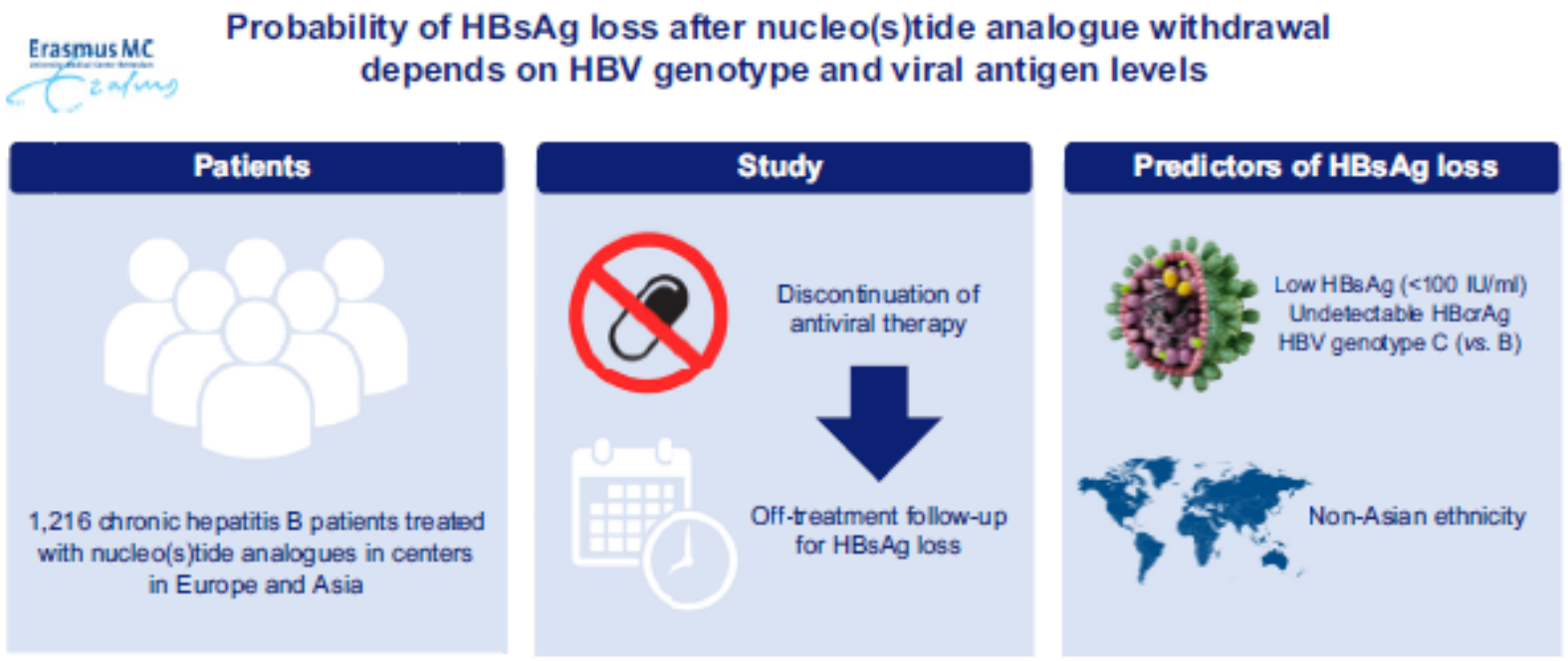
Table 2. HBsAg loss rate related to off-NUC events.

Event	HBV DNA (IU/mL)	ALT (U/L)	No of Patient	HBsAg Loss 6-Year Rate
Sustained response	<2000	N	144	36%
Virologic relapse	>2000	N	128	13%
Clinical relapse	>2000	>2 × ULN		
No-retreatment			150	19%
Re-treatment			269	1%
Total			691	13%

N: normal; ULN: upper limit of normal; data adapted from reference [48].

Probability of HBsAg loss after nucleo(s)tide analogue withdrawal depends on HBV genotype and viral antigen levels

Sonneveld et al Journal of Hepatology 2022



Overall HbsAg loss at wk 144:

8,1% patients

(22,9% non Asian vs 4,7% Asian)

Critères d'inclusion: ttmt/NUCs, HBe et DNA négatifs à l'arrêt, mesures AgHBs et AgHBcr

91% asiatiques, 7,5% caucasiens

41% géno B; 30% géno C et 6,7% geno D

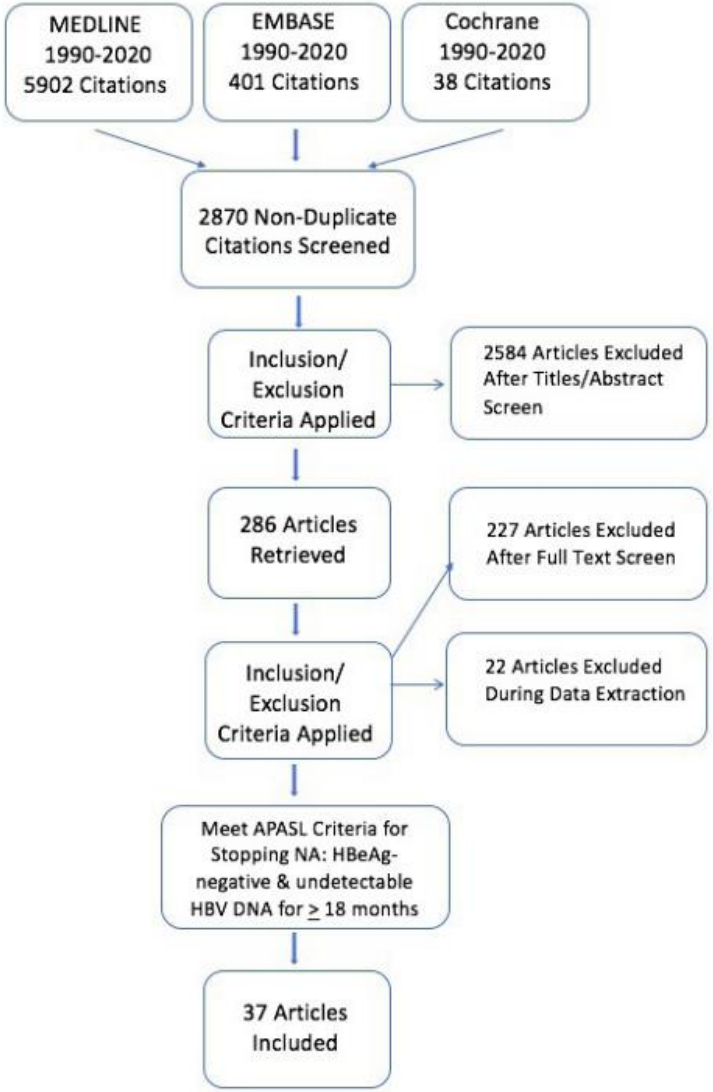
Durée ttmt mediane 167 semaines (156-294)

Original research

Gut 2022

Discontinuation of nucleot(s)ide analogue therapy in HBeAg-negative chronic hepatitis B: a meta-analysis

Samuel Anthony Lachlan Hall ,[1] Sara Vogrin,[2] Olivia Wawryk,[2] Gareth S Burns,[1] Kumar Visvanathan,[2,3] Vijaya Sundararajan,[4] Alexander Thompson[1,2]



What are the new findings?

⇒ Virological relapse is common after stopping NA therapy, but clinical relapse at 12 months was only seen in one-third of patients at 12 months.

⇒ The cumulative incidence of HBsAg loss was higher in cohorts with a median follow-up of >48 months (27%).

⇒ Hepatic decompensation and hepatocellular carcinoma were rare, but occurred more frequently in studies including cirrhotic individuals.

How might it impact on clinical practice in the foreseeable future?

⇒ Stopping NA therapy can be associated with higher rates of HBsAg clearance when this strategy is used in Caucasian patients and when individuals have longer follow-up (>36 months).

⇒ Serious adverse events can be minimised by reserving NA cessation for non-cirrhotic individuals.

⇒ Future studies should focus on the development of biomarkers to identify the most suitable candidates for this management strategy.

Traitement du VHB: quels challenges virologiques?

… de la suppression virale à l'éradication, en passant par la « guérison fonctionnelle »…

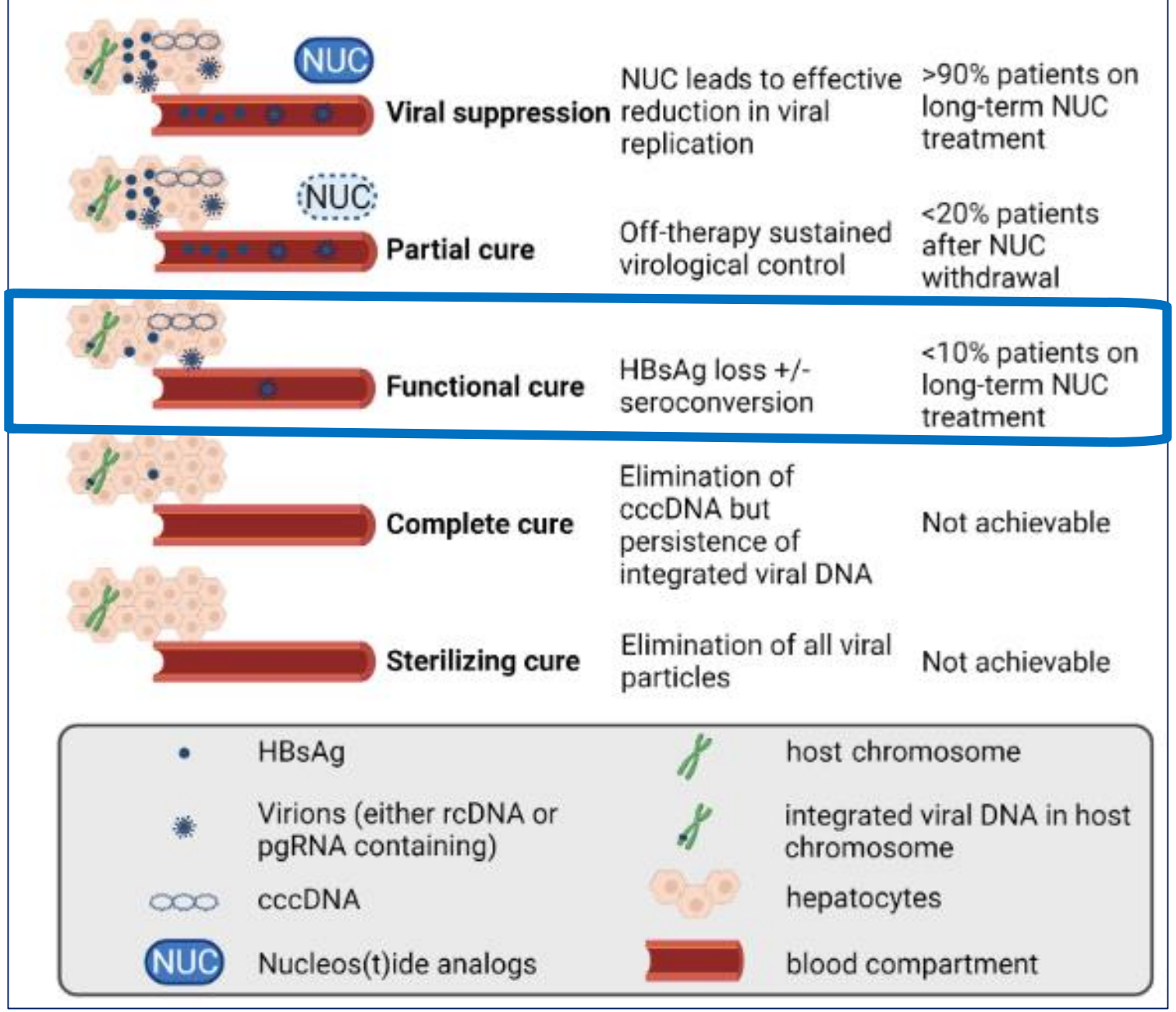
- réservoir cellulaire ccc-DNA
- échappement / épuisement du système immunitaire
- marqueurs de suivi ± informatifs

- atteindre le pool de ccc-DNA
- restaurer l'immunité spécifique
- assurer un suivi biologique pertinent

Guérison fonctionnelle

situation clinico-virologique où le traitement antiviral peut être arrêté sans risque de réactivation

Régression du risque de cirrhose et de CHC



Mak LY et al. Trends in Mol Med Sept 2022

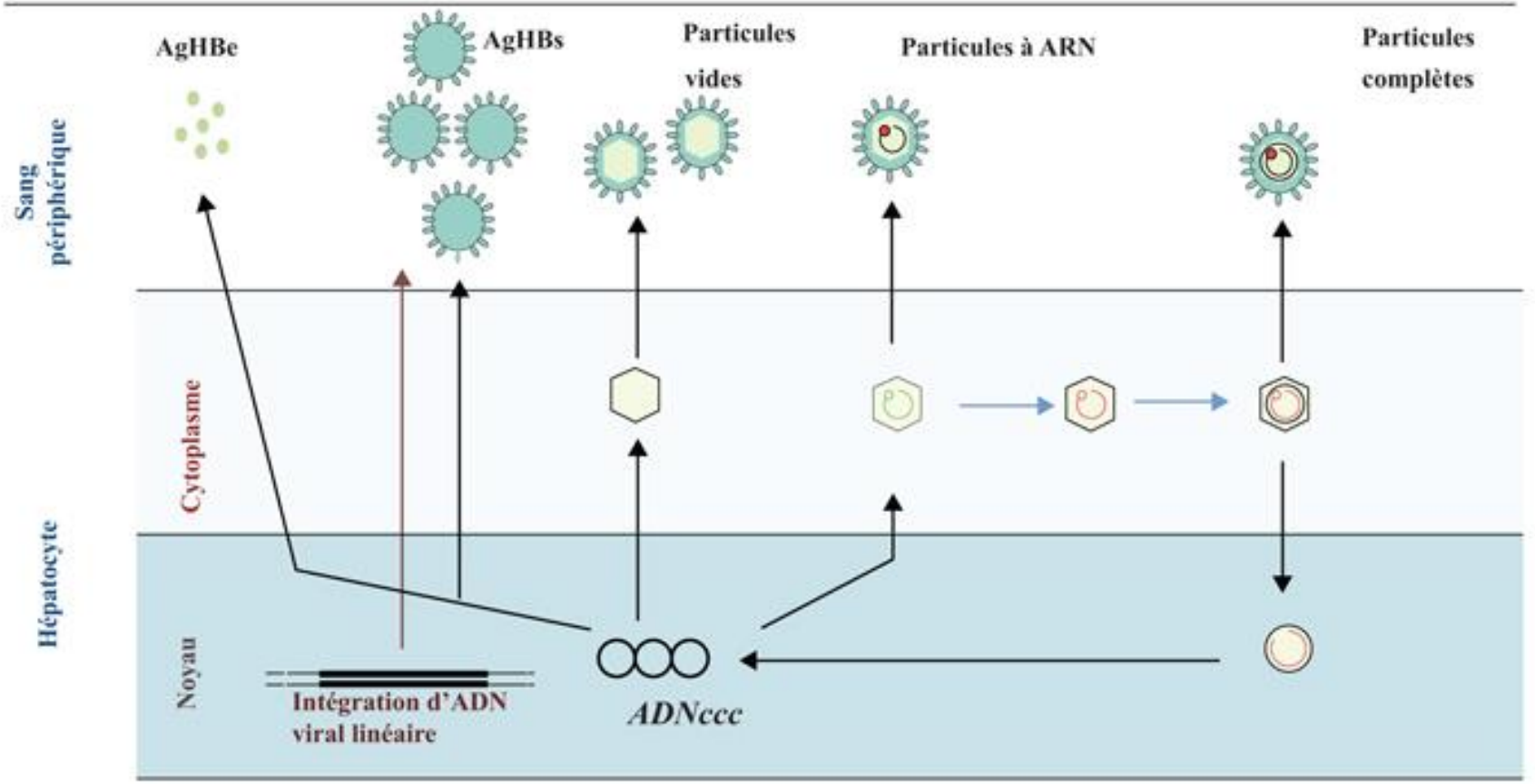
Marqueurs de suivi

Sofia Perez del Pulgar, 9th International HBV Cure ANRS-MIE Workshop July 2022
Slim Fourati, Virologie 2019

Marqueurs *supposés refléter* le réservoir viral du VHB

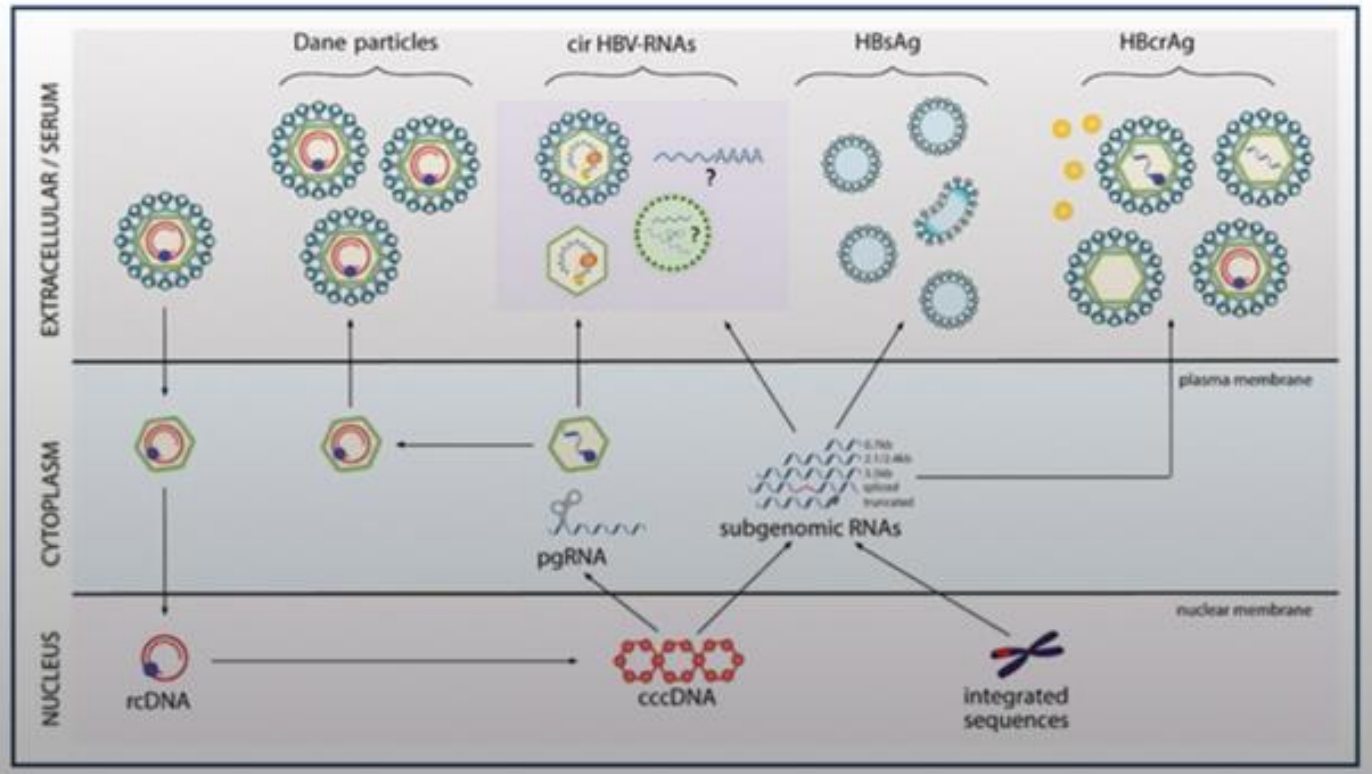
- ADNccc = « Le Marqueur » mais non accessible en pratique courante
- AgHBs: activité transcriptionnelle de ADNccc et de l'ADN intégré
- AgHBcr: activité transcriptionnelle de ADNccc
- ARN-VHB circulant (cirHBV-RNAs): nature controversée mais corrélation ADNccc

Marqueurs virologiques sériques	AgHBe	AgHBs	Particules vides	Particules à ARN	Particules complètes
Ag HBs quantitatif		+	+	+	+
HBcrAg	+		+	+	+
ARN VHB				+	



Fourati S, 2019

Why do we need to monitor cccDNA?



Template for all viral transcripts

cccDNA amount and transcriptional activity is important for disease progression and clinical outcomes

Adapted from Testoni B et al. Semin Liver Dis. 2017

HBsAg, the classical marker

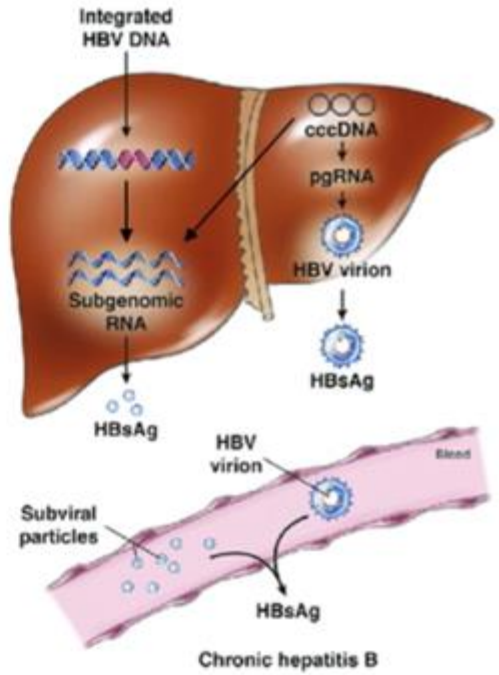
- HBsAg can be derived from cccDNA and integrated HBV DNA (i.e. HBeAg- patients)

Wooddell CI et al. Sci Transl Med 2017
Freitas N et al. J Virol. 2018

- HBsAg loss = functional cure → TOP TOP clinical endpoint!

- Low HBsAg is the best predictor of successful outcome after NA discontinuation

Liu J et al. Hepatology. 2019
Gao L et al. Ann Hepatol. 2020
Papatheodoridi M et al. J Viral Hep. 2020
Tseng TN et al. Clin Gastroenterol Hepatol. 2020
Sonneveld MJ et al. J Hepatol. 2022
... and quite a few others...



Adapted from Dusheiko G and Wang B. Gastroenterolog

HBcrAg

Biomarqueur composite: ensemble des produits de transcription du gène préC/C = AgHBc + Ag Hbe + précurseur protéique p22

- ? Différentiation portage chronique inactif/hépatite chronique
- ? Prédiction réponse au traitement
- ? Prédiction de la survenue à long terme d'un CHC
- ? Prédiction réactivation VHB

…La validation de l'intérêt clinique de ce test fait encore débat et nécessite des études plus approfondies…

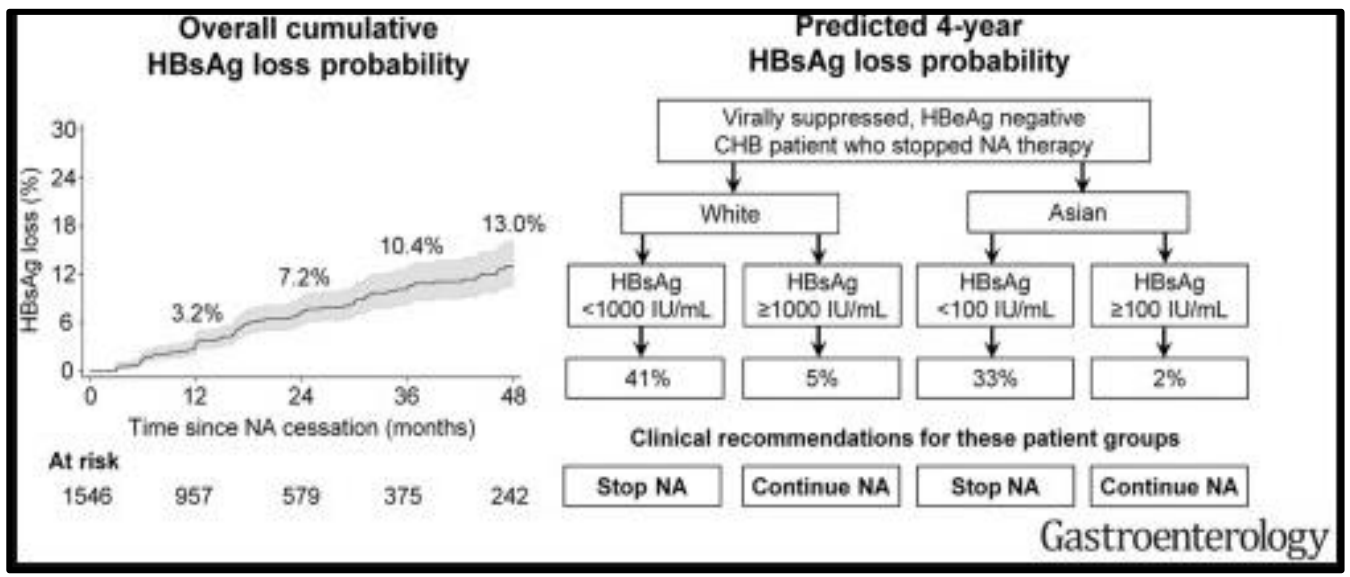
Gastroenterology
Volume 162, Issue 3, March 2022, Pages 757-771.e4

Original Research
Full Report: Clinical—Liver

Off-Therapy Response After Nucleos(t)ide Analogue Withdrawal in Patients With Chronic Hepatitis B: An International, Multicenter, Multiethnic Cohort (RETRACT-B Study)

Grishma Hirode [1, 2, 3], Hannah S.J. Choi [1, 2], Chien-Hung Chen [4], Tung-Hung Su [5], Wai-Kay Seto [6], Stijn Van Hees [7], Margarita Papatheodoridi [8], Sabela Lens [9], Grace Wong [10], Sylvia M. Brakenhoff [11], Rong-Nan Chien [12], Jordan Feld [1, 2, 3], Milan J. Sonneveld [11], Henry L.Y. Chan [10], Xavier Forns [9], George V. Papatheodoridis [8], Thomas Vanwolleghem [7], Man-Fung Yuen [6] ... Harry L.A. Janssen [1, 2, 3]

n = 1552 patients



Received: 3 November 2017 | Accepted: 28 December 2017
DOI: 10.1002/jmv.25028

SHORT COMMUNICATION

WILEY JOURNAL OF MEDICAL VIROLOGY

Very slow decline of hepatitis B virus surface antigen and core related antigen in chronic hepatitis B patients successfully treated with nucleos(t)ide analogues

Enagnon K. Alidjinou[1] | Charlotte Michel[1] | Valérie Canva[2] | Faïza Ajana[3] | Didier Hober[1] | Laurence Bocket[1]

[1] Univ Lille, Faculté de Médecine, CHU Lille, Laboratoire de Virologie EA3610, Lille, France
[2] CHU de Lille, Service des Maladies de l'Appareil Digestif, Lille, France
[3] CH Dron, Service Universitaire des Maladies Infectieuses, Tourcoing, France

Correspondence
Enagnon K. Alidjinou, Laboratoire de Virologie, Centre de Biologie Pathologie, CHU de Lille, Boulevard du Professeur Jules Leclercq, 59037 Lille, France.
Email: enagnonkazali.alidjinou@univ-lille2.fr

We investigated the decline of hepatitis B virus surface antigen (HBsAg) and core related antigen (HBcrAg) in chronic hepatitis B patients sussessfully treated with nucleos(t)ide analogues. In patients with plasma viral suppression, the baseline median levels of HBsAg and HBcrAg were 3.1 and 3.0 log U/mL, respectively. The levels in naïve patients were 4.2 and 3.6 log U/mL for HBsAg and HBcrAg, respectively. No significant decline was observed in patients with viral suppression within a year period. A low reduction was observed during the first months after treatment initiation, especially regarding HBcrAg. The dynamics of these antigens after viral suppression should be further investigated.

KEYWORDS
chronic hepatitis, HBcrAg, HBsAg, HBV, nucleos(t)ide analogues

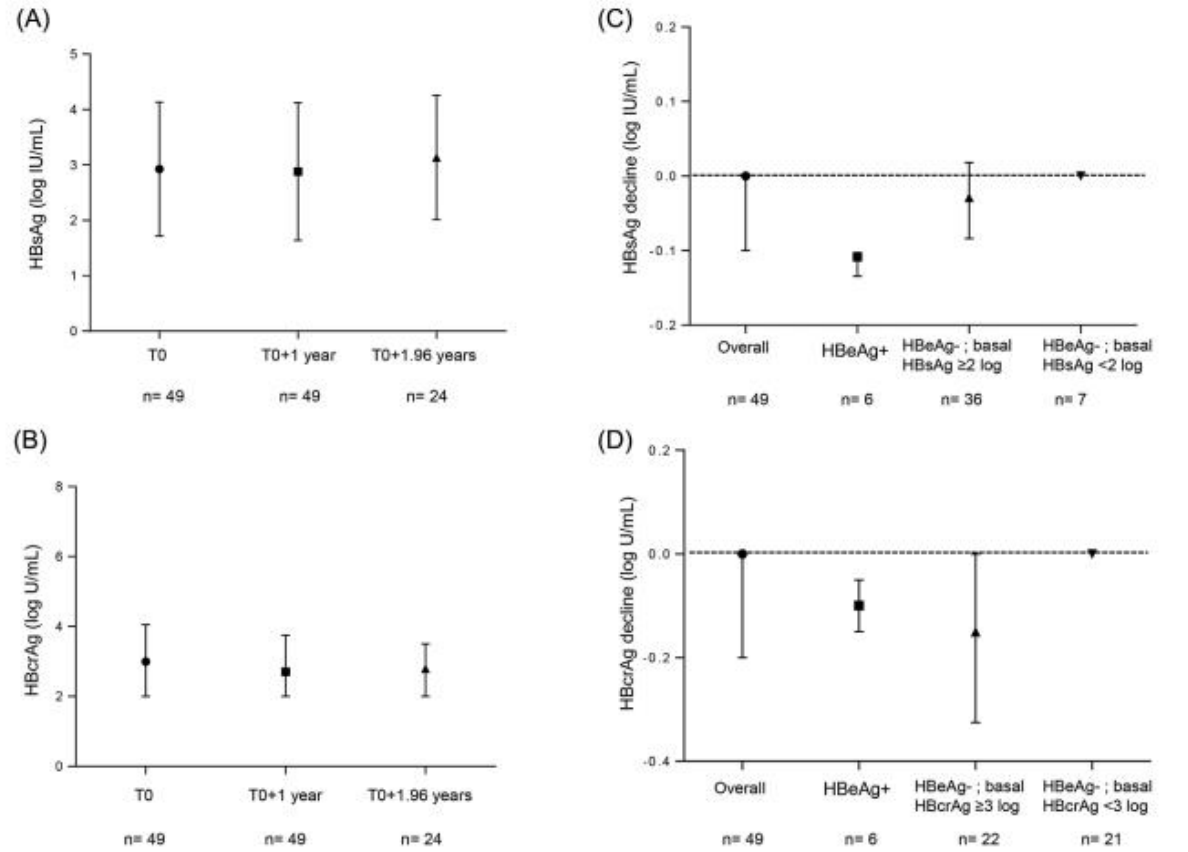


FIGURE 1 Kinetics of HBs and HBcr antigens in patients treated with nucleos(t)ide analogues. HBs and HBcr antigens were quantified at different time points in long-term treated patients with undetectable plasma HBV DNA (A, B). The decline in HBsAg (C) and HBcrAg (D) was shown for different groups of patients. Data are shown as median ± IQR

n = 49 pts sous ttmt / NUCs + 13 pts naifs initiant le ttmt

Meta-Analysis > Clin Gastroenterol Hepatol. 2021 Jan;19(1):46-60.e8.
doi: 10.1016/j.cgh.2020.04.045. Epub 2020 Apr 29.

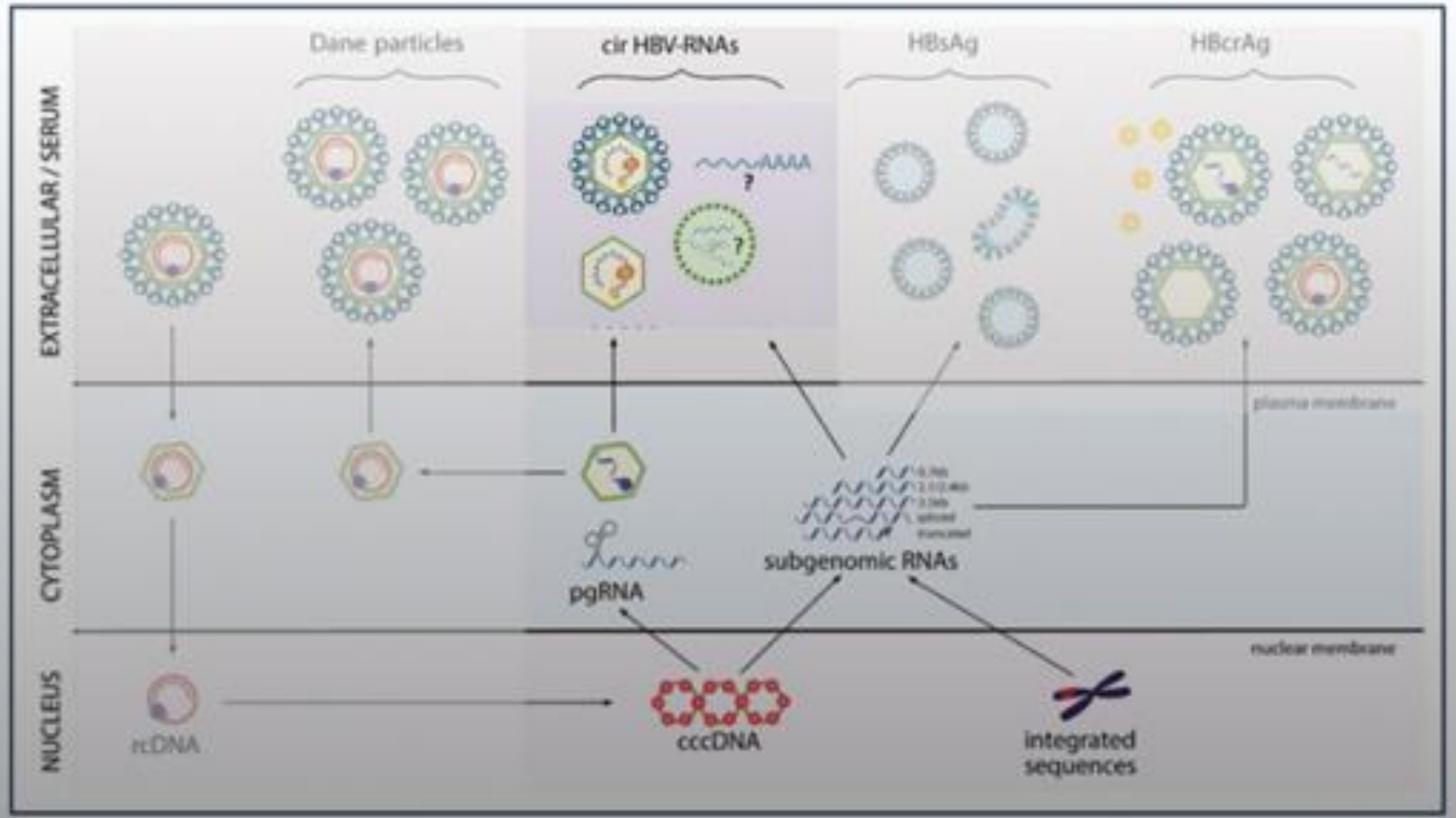
Hepatitis B Core-Related Antigen to Indicate High Viral Load: Systematic Review and Meta-Analysis of 10,397 Individual Participants

Kyoko Yoshida [1], Alice Desbiolles [2], Sarah F Feldman [2], Sang Hoon Ahn [3], Enagnon K Alidjinou [4], Masanori Atsukawa [5], Laurence Bocket [4], Maurizia R Brunetto [6], Maria Buti [7], Ivana Carey [8], Gian Paolo Caviglia [9], En-Qiang Chen [10], Markus Cornberg [11], Masaru Enomoto [12], Masao Honda [13], Christoph Höner Zu Siederdissen [11], Masatoshi Ishigami [14], Harry L A Janssen [15], Benjamin Maasoumy [11], Takeshi Matsui [16], Akihiro Matsumoto [17], Shuhei Nishiguchi [18], Mar Riveiro-Barciela [7], Akinobu Takaki [19], Pisit Tangkijvanich [20], Hidenori Toyoda [21], Margo J H van Campenhout [22], Bo Wang [8], Lai Wei [23], Hwai-I Yang [24], Yoshihiko Yano [25], Hiroshi Yatsuhashi [26], Man-Fung Yuen [27], Eiji Tanaka [28], Maud Lemoine [1], Yasuhito Tanaka [29], Yusuke Shimakawa [30]

Results: Of 74 eligible studies, IPD were obtained successfully for 60 studies (81%). Meta-analysis included 5591 IPD without antiviral therapy and 4806 treated with antivirals. In untreated patients, the pooled area under the receiver operating characteristic curve and optimal cut-off values were as follows: 0.88 (95% CI, 0.83-0.94) and 3.6 log U/mL to diagnose HBV DNA level of 2000 IU/mL or greater; and 0.96 (95% CI, 0.94-0.98) and 5.3 log U/mL for 200,000 IU/mL or greater, respectively. In the validation set, the sensitivity and specificity were 85.2% and 84.7% to diagnose HBV DNA level of 2000 IU/mL or greater, and 91.8% and 90.5% for 200,000 IU/mL or greater, respectively. The performance did not vary by HBV genotypes. In patients treated with anti-HBV therapy the correlation between HBcrAg and HBV DNA was poor.

Conclusions: HBcrAg might be a useful serologic marker to indicate clinically important high viremia in treatment-naïve, HBV-infected patients.

Circulating HBV-RNA



- The nature of circulating RNA-containing particles still remains controversial

Table 2. Potential Clinical Application of HBcrAg and HBV RNA in Chronic Hepatitis B Infection

Area of interest	HBcrAg	HBV RNA
Natural history		
Differentiate disease phases	+	+
Predicts spontaneous HBeAg seroconversion	+	No data
Predicts spontaneous HBsAg seroclearance	(–)*	No data
Antiviral treatment: PEG-IFN or NA		
Predict treatment-induced HBeAg seroconversion	+	+
Predict post-NA cessation flare	+	+
Clinical trials of new antiviral agents		
Dynamic change in siRNA	+	No data
Dynamic change in CpAM	No data	+
Dynamic change in RIG-I + NOD2 agonist	No data	+
Special populations		
Predict HCC development	+	No data
Predict reactivation of HBV under immunosuppression	+	No data
Profile in acute infection	No data	(–)†

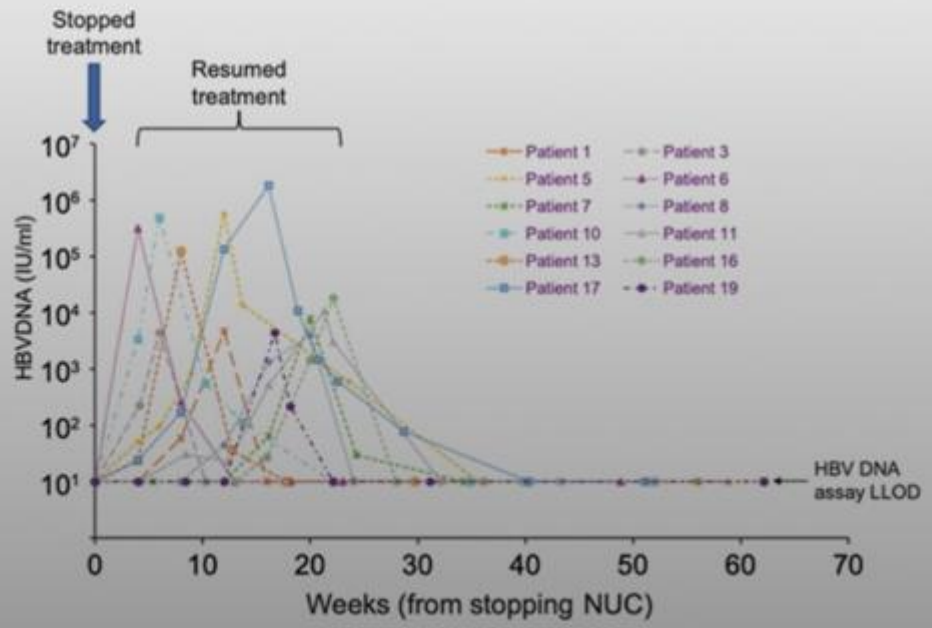
HBcrAg, hepatitis B core-related antigen; HBV, hepatitis B virus; HBeAg, hepatitis B virus e antigen; HBsAg, hepatitis B virus surface antigen; PEG-IFN, pegylated interferon; NA, nucleos(t)ide analogues; siRNA, short interfering RNA; CpAM, core protein allosteric modulators; RIG-I, retinoic acid-inducible gene I; NOD2, nucleotide-binding oligomerization domain-containing protein 2; HCC, hepatocellular carcinoma.

*Profile of HBcrAg reported in patients with HBsAg seroclearance, but no further data on predictive power; †Only data on 2 patients with acute HBV infection was reported (see text).

Mak LY et al, Gut and Liver 2019

Absence of cccDNA/cirB-RNA does not exclude viral rebound

13 patients with undet cccDNA → STOP NUCs → HBV-DNA rebound in all patients



Baseline:
HBV-RNA undet in all patients
HBcrAg+: 4 patients

Lai CL et al, JHEP Rep. 2020

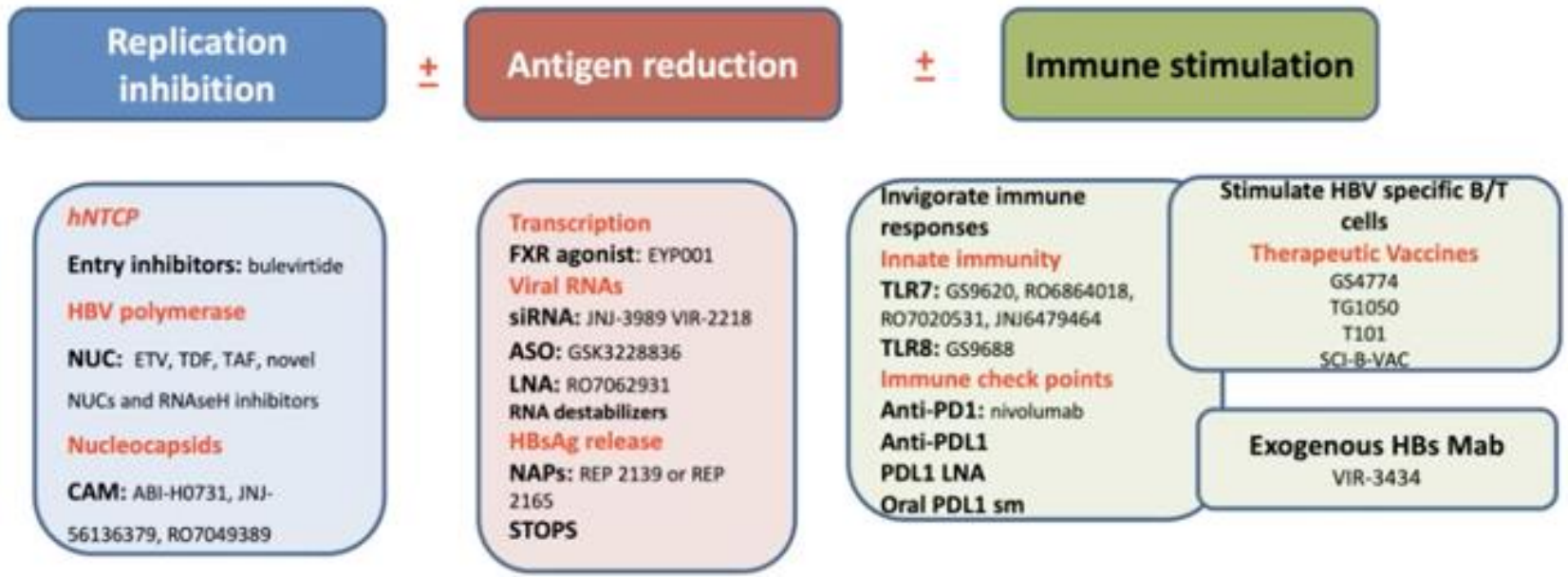
En résumé

- Ag HBs quantifié actuel marqueur de suivi
- Ag HBcr serait un bon marqueur de l'activité transcriptionnelle cccDNA
- AgHBcr et cir HBV-RNAs
  - pertinence clinique à évaluer
  - techniques à standardiser
- Nécessité de distinguer ccc-DNA et séquences virales intégrées
- Apport pour recherche et évaluation thérapeutique

? Seuils ?
HBsAg 1,9 log et HBcrAg 3 log

HBV CURE

New Concepts of Combination Therapy to Cure HBV

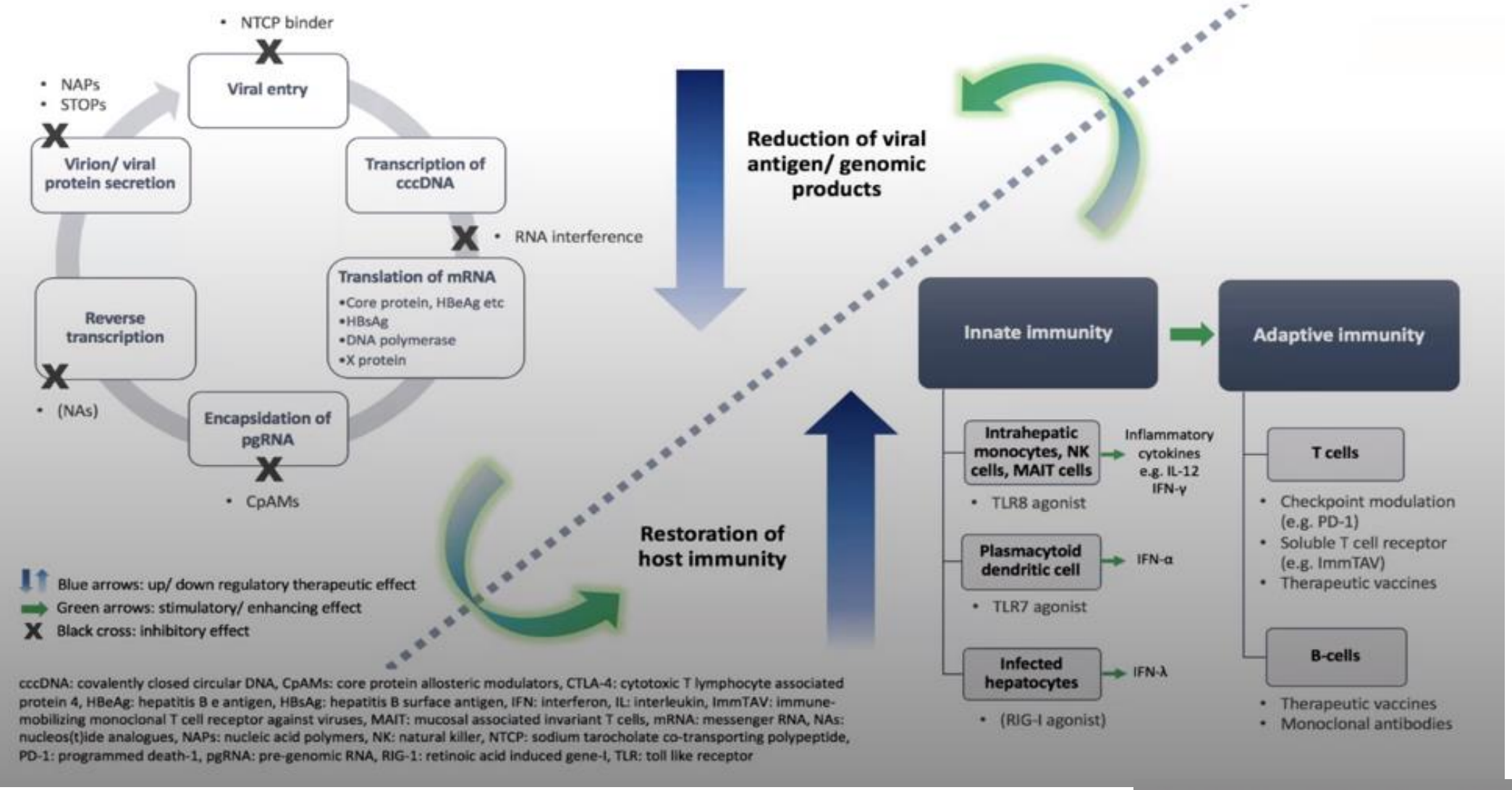


ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Fanning et al. Nat Rev Drug Discov. 2019 Nov;18(11):827-844; Roca Suarez et al, Liver International 2021

Reference site:
www.hepb.org/treatment-and-management/drug-watch/

Novel agents to enhance functional cure: Targeting the virus vs. Enhancing immune response



cccDNA: covalently closed circular DNA, CpAMs: core protein allosteric modulators, CTLA-4: cytotoxic T lymphocyte associated protein 4, HBeAg: hepatitis B e antigen, HBsAg: hepatitis B surface antigen, IFN: interferon, IL: interleukin, ImmTAV: immune-mobilizing monoclonal T cell receptor against viruses, MAIT: mucosal associated invariant T cells, mRNA: messenger RNA, NAs: nucleos(t)ide analogues, NAPs: nucleic acid polymers, NK: natural killer, NTCP: sodium tarocholate co-transporting polypeptide, PD-1: programmed death-1, pgRNA: pre-genomic RNA, RIG-1: retinoic acid induced gene-I, TLR: toll like receptor

Mak LY, Seto WK & Yuen MF. Viruses 2021;13:1169

Nouveaux traitements antiviraux

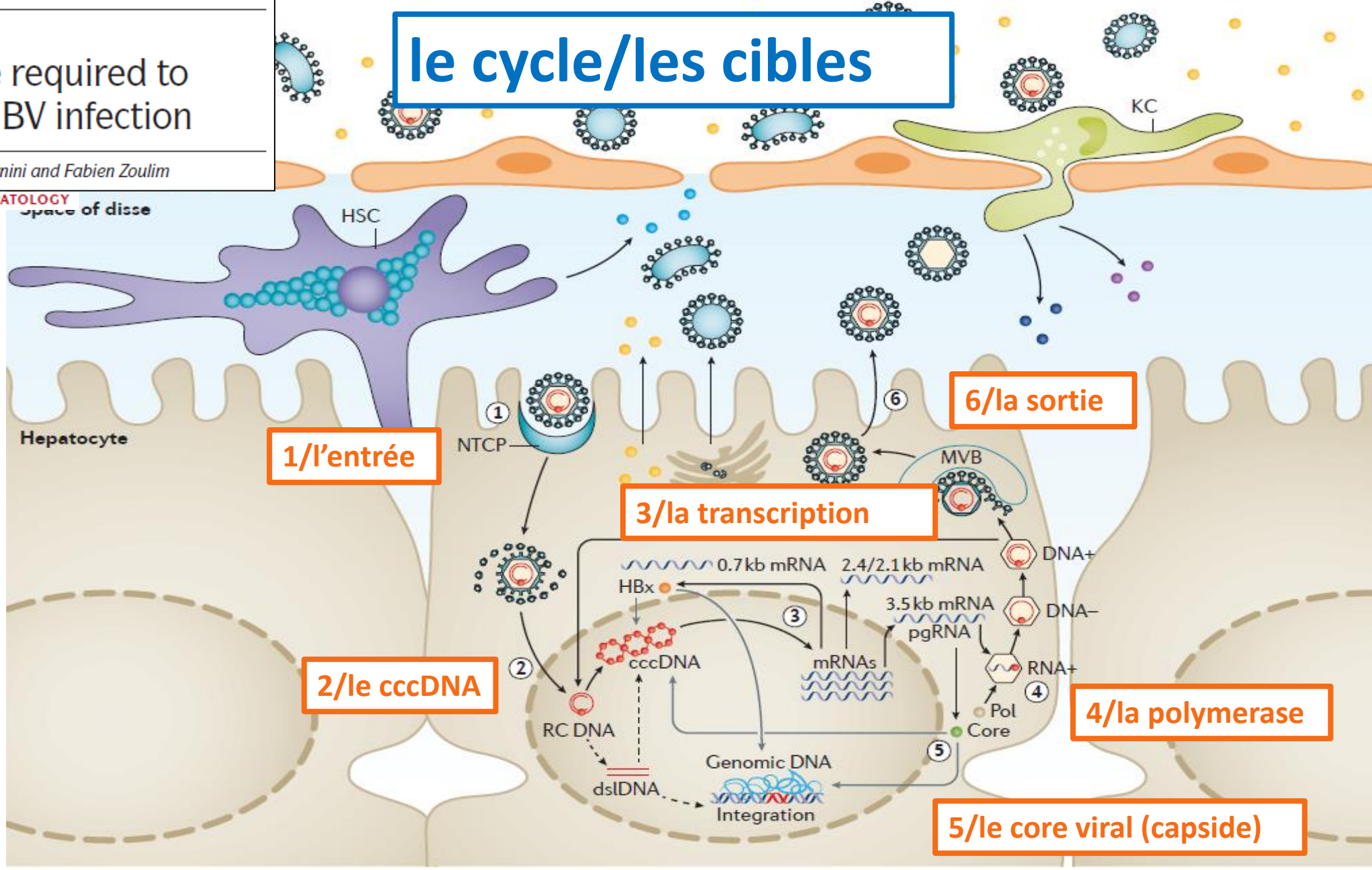
OPINION

Global strategies are required to cure and eliminate HBV infection

Peter Revill, Barbara Testoni, Stephen Locarnini and Fabien Zoulim

NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY

le cycle/les cibles



doi:10.1038/nrgastro.2016.7
Published online 24 Feb 2016;
corrected online 17 March 2016

HBV

Subviral particles composed of HBV genome-free enveloped capsids

Subviral particles (SVP) composed of HBV envelope proteins (spheres)

Subviral particles (SVP) composed of HBV envelope proteins (filaments)

HBe
TGFβ
IL6
IFNβ
HBs

FAMILY/DRUG NAME	MECHANISM	COMPANY	WEBSITE	USA STATUS
Interferons: Mimic infection-fighting immune substances naturally produced in the body				
Intron A (Interferon alfa 2b)	Immunomodulator	Merck, USA	merck.com	Approved 1991
Pegasys (Peginterferon alfa 2a)	Immunomodulator	Genentech, USA	gene.com	Approved 2005
Nucleos(t)ide Analogues: Interfere with viral DNA polymerase used for HBV replication				
Epivir (Lamivudine) **Generics available*	Inhibits viral DNA polymerase	GlaxoSmithKline (GSK)	gsk.com	Approved 1998
Hepsera (Adefovir dipivoxil) **Generics available*	Inhibits viral DNA polymerase	Gilead Sciences, USA	gilead.com	Approved 2002
Baraclude (Entecavir) **Generics available*	Inhibits viral DNA polymerase	Bristol-Myers Squibb, USA	bms.com	Approved 2005
Tyzeka (Telbivudine) **Generics available*	Inhibits viral DNA polymerase	Novartis, USA	novartis.com	Approved 2006
Viread (Tenofovir) **Generics available*	Inhibits viral DNA polymerase	Gilead Sciences	gilead.com	Approved 2008
Vemlidy (TAF or tenofovir alfenamide)	Prodrug of Tenofovir	Gilead Sciences	gilead.com	Approved 2016
Levovir (Cledvudine)	Inhibits viral DNA polymerase	Bukwang, S. Korea	bukwang.co.kr	Approved 2006 in S. Korea
Besivo (formerly ANA 380/LB80380)	Inhibits viral DNA polymerase	Ildong Pharma, S. Korea	ildong.com	Approved 2017 in S. Korea
Zadaxin	Immunomodulator	SciClone, USA	sciclone.com	Approved outside USA
ATI-2173 (Clevudine prodrug)	Inhibits HBV polymerase	Antios Therapeutics, USA	antiostherapeutics.com	FDA Hold

www.hepb.org/treatment-and-management/drug-watch/

Direct Acting Antivirals: Targets the virus and interferes in the HBV replication process				
Silencing RNA's (siRNAs): Interferes and destroys viral RNA				
VIR-2218	RNAi gene silencer	Vir Biotech, USA	vir.bio	Phase II
RG6346 (DCR HBVS)	RNAi gene silencer	Dicerna with Roche	dicerna.com	Phase II
JNJ-3989	RNAi gene silencer	J&J with Arrowhead, USA	arrowheadpharma.com	Phase II
AB-729	RNAi gene silencer	Arbutus Biopharma, USA	arbutusbio.com	Phase II
ALG-125755	RNAi gene silencer	Aligos Therapeutics, USA	aligos.com	Phase I
BB-103	RNAi gene silencer	Benitec, Australia	benitec.com	Preclinical
Entry Inhibitors: Interferes with HBV getting into liver cells				
Hepcludex (Bulevirtide)	Entry inhibitor	Gilead, USA	Gilead.com	Phase II/III
hzVSF (IgG4)	Entry inhibitor	ImmuneMed, South Korea	immunemed.co.kr/eng	Phase II
A2342	Entry inhibitor	Albireo, USA	albireopharma.com	Preclinical

Capsid or Core Inhibitors: Interferes with the viral DNA protein shield				
Morphothiadin	Capsid inhibitor	HEC Pharma, PR China	pharm.hec.cn/en/	Phase II
JNJ 56136379	Capsid inhibitor	Janssen, Ireland	janssen.com	Phase II
EDP-514	Capsid inhibitor	Enanta Pharma, USA	enanta.com	Phase I
RG7907	Capsid inhibitor	Roche, Switzerland	roche.com	Phase I
QL-007	Capsid inhibitor	Qilu, PR China	en.qilu-pharma.com	Phase I
ABI-H3733	Capsid inhibitor	Assembly Biosciences, USA	assemblybio.com	Phase I
Canocapavir (ZM-H1505R)	Capsid inhibitor	Zhimeng Biopharma, PR China	core-biopharma.com	Phase I
ALG-000184	Capsid inhibitor	Aligos Therapeutics, USA	aligos.com	Phase I
AB-836	Capsid inhibitor	Arbutus, USA	arbutusbio.com	Phase I
VNRX-9945	Capsid inhibitor	Venatorx, USA	venatorx.com	Phase I
GLP-26	Capsid inhibitor	Emory University, USA	emory.edu	Preclinical
ABI-4334	Capsid inhibitor	Assembly Biosciences, USA	assemblybio.com	Preclinical
ATI-1428	Capsid inhibitor	Antios Therapeutics, USA	antiostherapeutics.com	Preclinical

www.hepb.org/treatment-and-management/drug-watch/

Direct Acting Antivirals: Targets the virus and interferes in the HBV replication process				
HBsAg Inhibitors: Interferes with production of HBV surface antigen (sAg)				
REP 2139	sAg inhibitor	Replicor, Canada	replicor.com	Phase II
BJT-574	sAg inhibitor	Blue Jay Therapeutics, USA	bluejaytx.com	Preclinical
Antisense Molecules: Binds to the viral mRNA to prevent it from turning into viral protein				
Bepirovirsen (GSK 3228836)	(ASO) Antisense oligonucleotide	GSK, USA	gsk.com	Phase II
GSK 4388067A	ASO combination	GSK, USA	gsk.com	Phase II
Gene Editing: Intended to destroy or repress HBV DNA				
EBT107	CRISPR/Cas 9	Excision Bio, USA	excisionbio.com	Preclinical
PBGENE-HBV	ARCUS platform	Precision Bio, USA	precisionbiosciences.com	Preclinical

www.hepb.org/treatment-and-management/drug-watch/

Modulation du système immunitaire

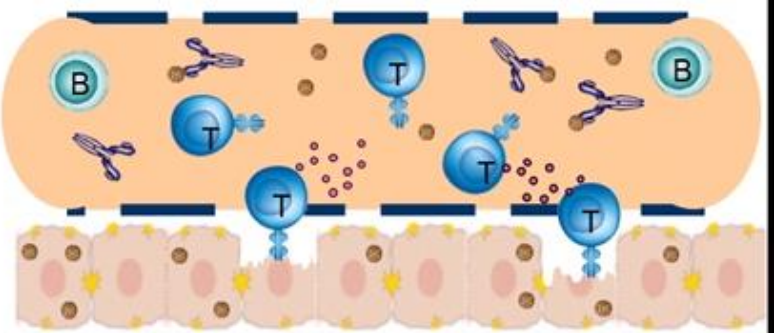
Rationale for Immunological Targets

To date, elimination (control) of HBV infection has only been achieved by the immune system.

Successful immune response is well characterized in resolution of acute infection

- **Innate immunity** – innate cytokines display antiviral function: IFN-α, IL-12, IL-18
- **Adaptive immunity** – coordinated, robust CD4 & CD8 T cell and B cell response
  - CD4 T cells are required for effective CD8 T cell differentiation
  - IFN-γ-mediates non-cytolytic reduction of HBV replication
  - Cytotoxic T cells eliminate infected hepatocytes
  - Antibody mediated clearance of circulating virus and antigen

Objective for immunotherapy in chronic hepatitis B has been to restore the level of immune function observed during resolution of acute infection



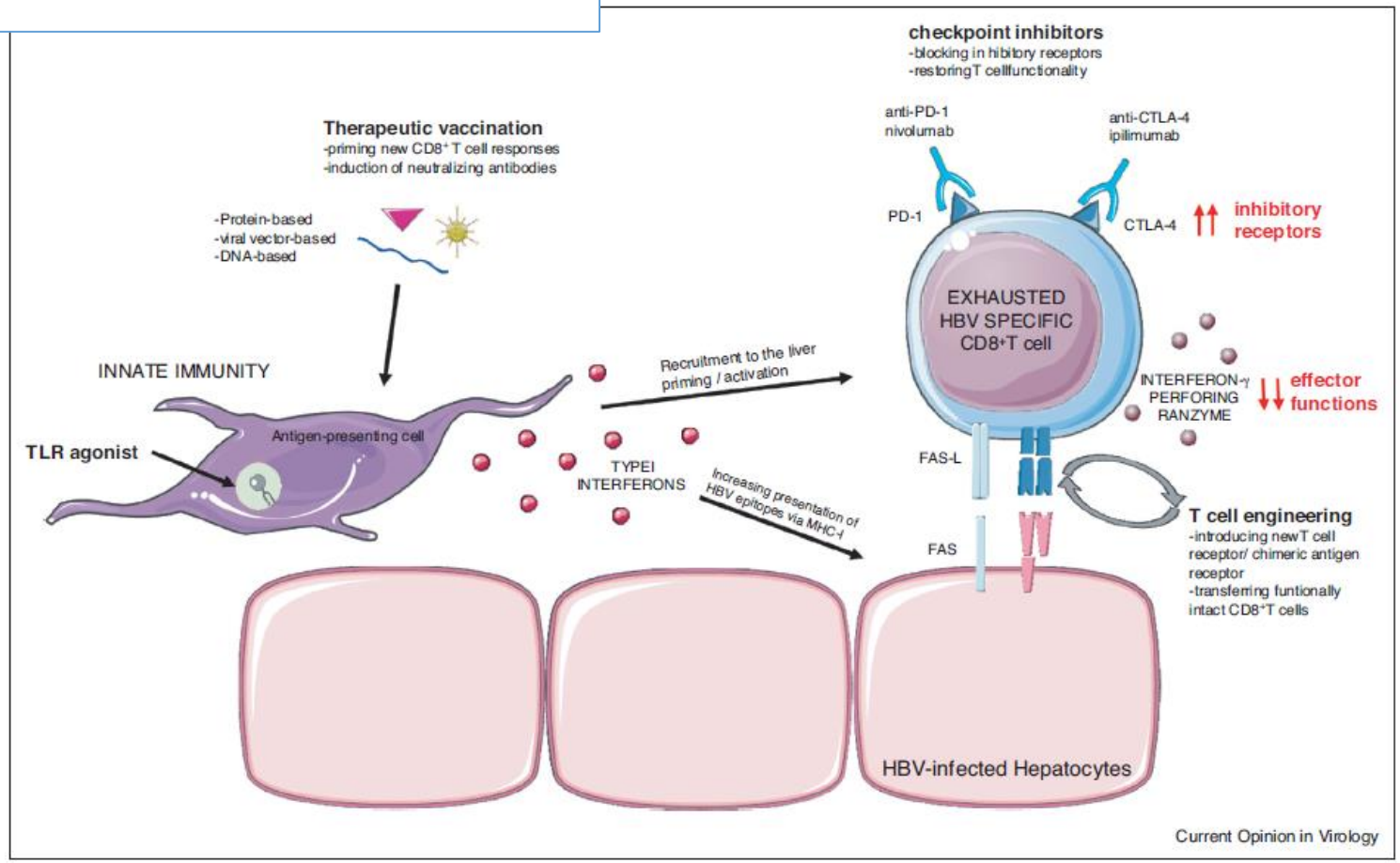
Erasmus MC
University Medical Center Rotterdam

TORONTO CENTRE FOR LIVER DISEASE

Immunotherapy and therapeutic vaccines for chronic HBV infection

Julia Lang-Meli[1,2], Christoph Neumann-Haefelin[1] and Robert Thimme[1]

Current Opinion in Virology 2021, **51**:149–157



Overview of immunotherapeutic concepts for chronic HBV infection with different objectives: to restore dysfunctional HBV-specific immune responses (e.g., checkpoint inhibitors and TLR7 agonist); to replace dysfunctional CD8 + T-cell responses (e.g., T-cell engineering); to induce novel HBV-specific immune responses (e.g., therapeutic vaccination). Images were provided by "smart.servier.com" under a Creative Commons Attribution 3.0 Unported License.

Immunologicals: Targets the human immune system to attack the HBV virus				
Therapeutic Vaccine Technology used to stimulate the immune system as a treatment				
HerberNasvac	Therapeutic vaccine	CIGB, Cuba	Clinical trials in Cuba	Phase IV
GS-4774	Therapeutic vaccine	Gobelmmune with Gilead, USA	globeimmune.com	Phase II
HepTcell	Therapeutic vaccine	Altimmune, USA	altimmune.com	Phase II
VBI-2601 (BRII-179)	Therapeutic vaccine	VBI Vaccines, USA	vbivaccines.com	Phase II
VVX001	Therapeutic vaccine	Viravaxx, Austria	viravaxx.com	Phase II
GSK 3528869A	Therapeutic vaccine	GSK, USA	gsk.com	Phase II
VTP-300	Therapeutic vaccine	Vaccitech, UK	vaccitech.co.uk	Phase II
CVI-HBV-002	Therapeutic vaccine	Cha Vaccine Institute, S. Korea	en.chavaccine.com	Phase I/II
AIC 649	Therapeutic vaccine	AiCuris, Germany	aicuris.com	Phase I/II
HB-110	Therapeutic vaccine	Ichor Medical with Genexine, USA	ichorms.com	Phase I
JNJ 64300535	Therapeutic vaccine	Ichor Medical with Janssen	ichorms.com	Phase I
CARG-201	Therapeutic vaccine	CaroGen, USA	carogencorp.com	Preclinical
Chimigen HBV	Therapeutic vaccine	Akshaya, Canada	akshayabio.com	Preclinical
HBV	Therapeutic vaccine	HOOKIPA Pharma, Austria, with Gilead	hookipapharma.com	Preclinical
TherVacB	Therapeutic vaccine	Helmholtz Zentrum Muenchen, Germany	thervacb.eu	Preclinical
PRGN-2013	Therapeutic vaccine	Precigen	precigen.com	Preclinical
ISA104	Therapeutic vaccine	ISA Pharma, The Netherlands	isa-pharma.com	Preclinical
VRON-0200	Therapeutic vaccine	Viron Therapeutics, USA	viriontx.com	Preclinical
CLB-3000	Therapeutic vaccine	Clear B Therapeutics, USA and Australia	clearbtherapeutics.com	Preclinical
"Decoy 20"	Therapeutic vaccine	Indaptus Therapeutics, USA	indaptusrx.com	Preclinical

www.hepb.org/treatment-and-management/drug-watch/

Immunologicals: Targets the human immune system to attack the HBV virus				
Compounds that activate the innate immune system				
Selgantolimod (GS9688)	TLR-8 agonist	Gilead Sciences, USA	gilead.com	Phase II
RG7854	TLR-7 agonist	Roche, Switzerland	roche.com	Phase I
CB06	TLR-8 agonist	Zhimeng Biopharma, PR China	core-biopharma.com	Phase I
SBT 8230	TLR-8 agonist	Silverback Therapeutics, USA	silverbacktx.com	Preclinical
YS-HBV-002	Activator of TLR3, RIG1, MDA5	YiSheng Biopharma, China	yishengbio.com	Preclinical
Monoclonal Antibodies: Neutralize or bind the HBV proteins to reduce infection				
Lenvervimab (GC1102)	Monoclonal antibody	GC Pharma, South Korea	globalgreencross.com	Phase II
VIR-3434	Monoclonal antibody	Vir Biotech, USA	vir.bio	Phase II
BJT-778	Monoclonal antibody	Blue Jay Therapeutics, USA	bluejaytx.com	Preclinical
Checkpoint Inhibitors: Stimulate exhausted T-cell recognition of HBV-infected cells				
ASC22 (KN035 or Envafolimab)	PDL1 inhibitor	Ascletis Pharma, PR China	ascletis.com	Phase II
GS 4224	PDL1 inhibitor	Gilead, USA	gilead.com	Phase I
RG6084	PDL1 inhibitor	Roche	roche.com	Phase I
Other Immunologicals				
IMC-I109V	T-cell Receptor	Immunocore	immunocore.com	Phase I
LT-V11	T-cell immunotherapy	Lion TCR, Singapore	liontcr.com	Preclinical

www.hepb.org/treatment-and-management/drug-watch/

Additional HBV Drugs Under Investigation				
APG-1387	Apoptosis inducer	Ascentage, PR China	ascentagepharma.com	Phase II
ASC42	FXR Agonist	Ascletis, Hong Kong	ascletis.com	Phase II
EYP001	FXR agonist	Enyo Pharma, France	enyopharma.com	Phase II
GV1001	"Novel peptide"	GemVax & KAEL, South Korea	gemvax.com	Preclinical
DF-006	Small molecule	Drug Farm, Shanghai	drug-farm.com	Preclinical
HBV	"IFNAR"	Assembly Biosciences, USA	assemblybio.com	Preclinical

www.hepb.org/treatment-and-management/drug-watch/

CONCLUSION

- recherche à la hauteur du challenge…

- taux de guérison fonctionnelle faible avec les traitements actuels … mais résultats prometteurs:
  - RNA inhibition
  - CpAM
  - HBsAg entry inhibitors + PegIFN
  - HBSAg release inhibitors + NA + PegIFN
  - Anticorps neutralisants
  - Aspin (NUCs à mode d'action différent) ± TDF

- marqueurs virologiques à améliorer

- ? résistance ?

Merci de votre attention

anrs MALADIES INFECTIEUSES ÉMERGENTES Inserm

ICE-HBV International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

IP-cure-B

RB-RNA