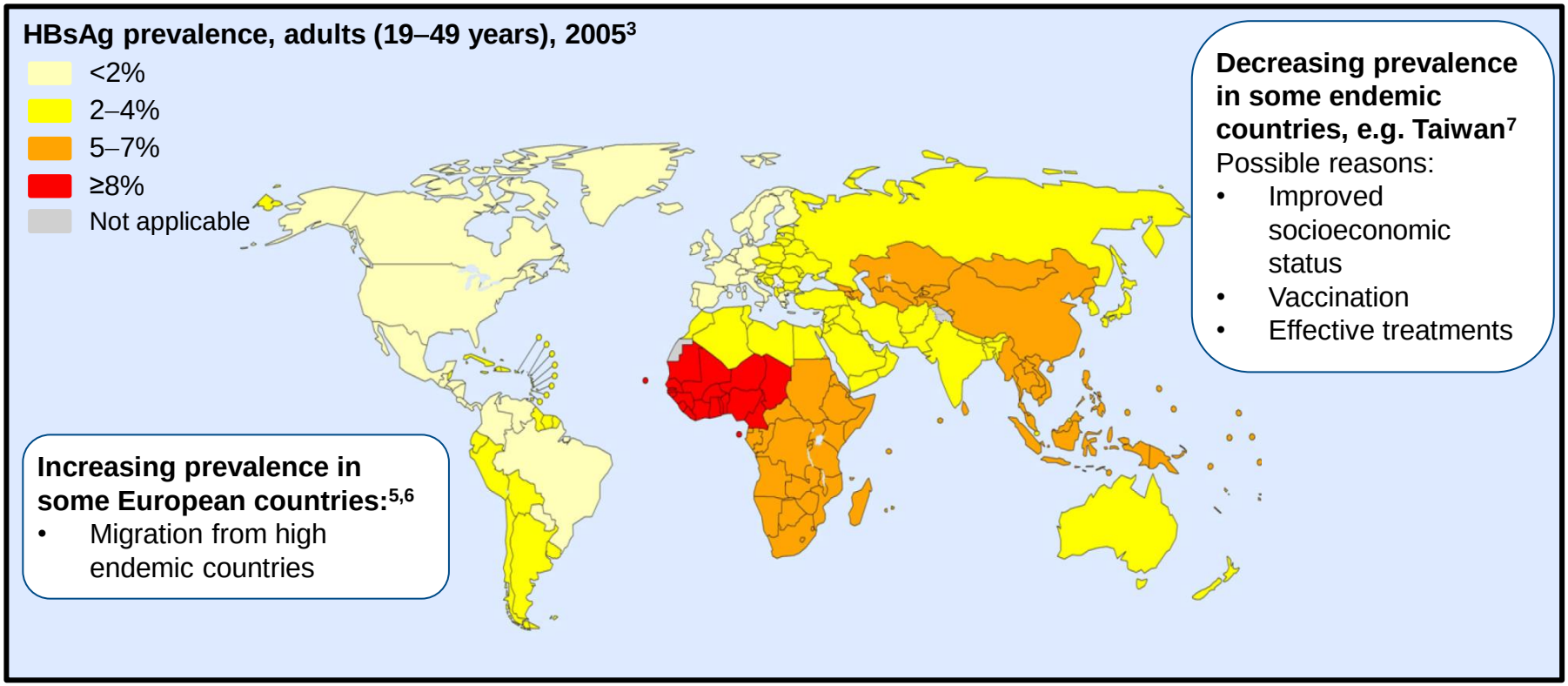
الجديد في التهاب الكبد HBV

د.ابتسام البوشي

مشفى دمشق

Epidemiology and public health burden[1]

- Worldwide ≈250 million chronic HBsAg carriers[2,3]
- 686,000 deaths from HBV-related liver disease and HCC in 2013[4]



1. EASL CPG HBV. J Hepatol 2017;67:370–98; 2. Schweitzer A, et al. Lancet 2015;386:1546–55;
3. Ott JJ, et al. Vaccine 2012;30:2212–9; 4. GBD 2013 Mortality and Causes of Death Collaborators. Lancet 2015;385:117–71;
5. Coppola N, et al. Euro Surveill 2015;20:30009; 6. Hampel A, et al. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2016;59:578–83; 7. Chen C-L, et al. J Hepatol 2015;63:354–63.

EASL™ The Home of Hepatology

New nomenclature for chronic phases

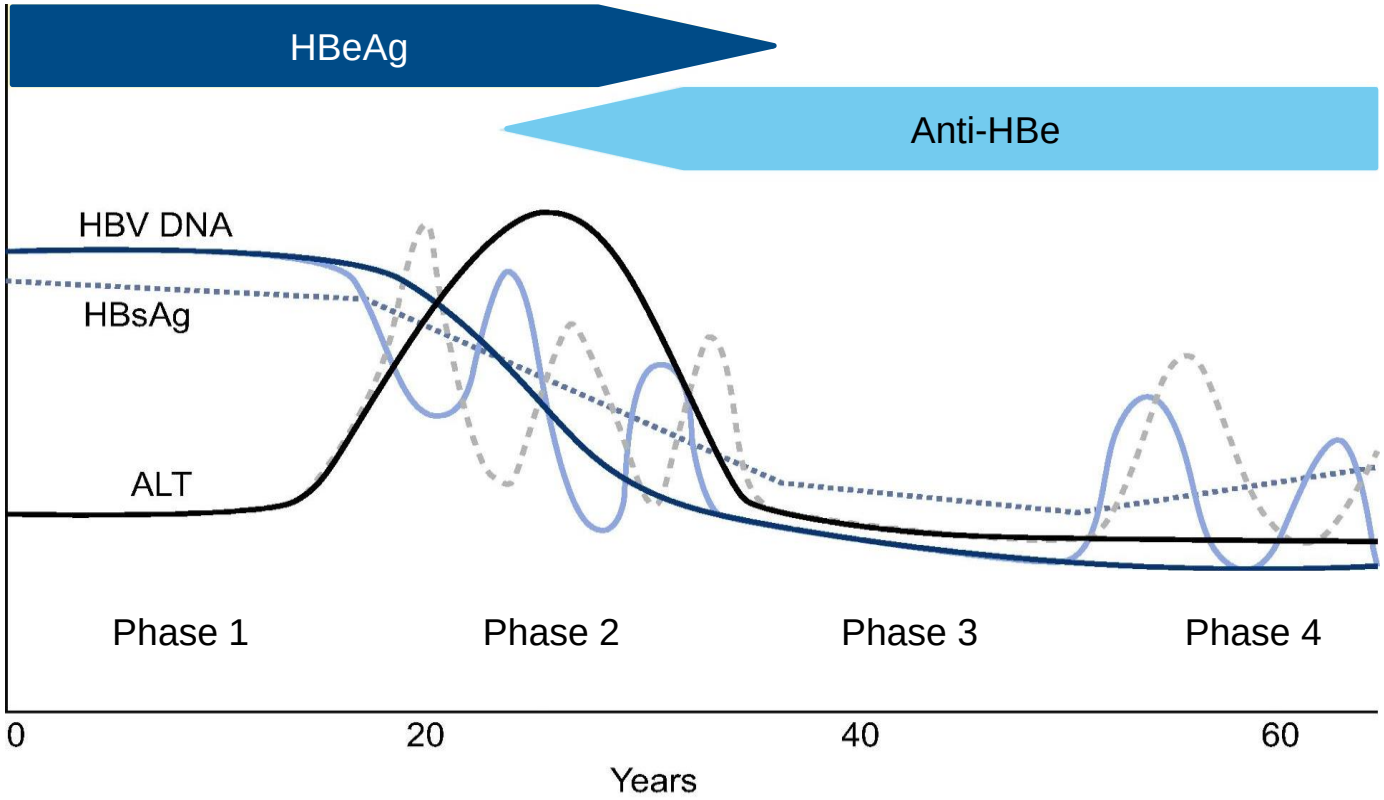
- The natural history of chronic HBV infection has been schematically divided into five phases

Chronic hepatitis B / Chronic HBV infection	HBeAg positive		HBeAg negative		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B	Resolved HBV infection
HBsAg	High	High/ intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	>10^7 IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL	<10 IU/mL‡
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liver disease	None/minimal	Moderate/ severe	None	Moderate/ severe	None§
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis	HBsAg negative /anti-HBc positive

*HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis;
†Persisitently or intermittently, based on traditional ULN (~40 IU/L). ‡cccDNA can frequently be detected in the liver;
§Residual HCC risk only if cirrhosis has developed before HBsAg loss.
EASL CPG HBV. J Hepatol 2017;67:370–98

EASL™ The Home of Hepatology

Phases of chronic HBV infection[1]



New nomenclature[2]	HBeAg-positive chronic HBV infection	HBeAg-positive chronic hepatitis B	HBeAg-negative chronic HBV infection	HBeAg-negative chronic hepatitis B

1. Lok A, et al. J Hepatol 2017;67:847–61;
2. EASL CPG HBV. J Hepatol 2017;67:370–98

Goals and endpoints of therapy

Goals

- Improve survival and quality of life by preventing disease progression and HCC
- Prevent mother-to-child transmission, hepatitis B reactivation, and prevent and treat HBV-associated extrahepatic manifestations

Recommendations	Grade of evidence	Grade of recommendation
Main endpoint • Induction of long-term suppression of HBV DNA	I	1
Valuable endpoint • Induction of HBeAg loss (± anti-HBe seroconversion) in HBeAg-positive patients with chronic hepatitis B*	II-1	1
Additional endpoint • ALT normalization (biochemical response)†	II-1	1
Optimal endpoint • HBsAg loss (± anti-HBs seroconversion)‡	II-1	1

*Often represents a partial immune control of the chronic HBV infection;
†Achieved in most patients with long-term suppression of HBV replication;
‡Indicates profound suppression of HBV replication and viral protein expression
EASL CPG HBV. J Hepatol 2017;67:370–98

EASL™ The Home of Hepatology

Indications for treatment

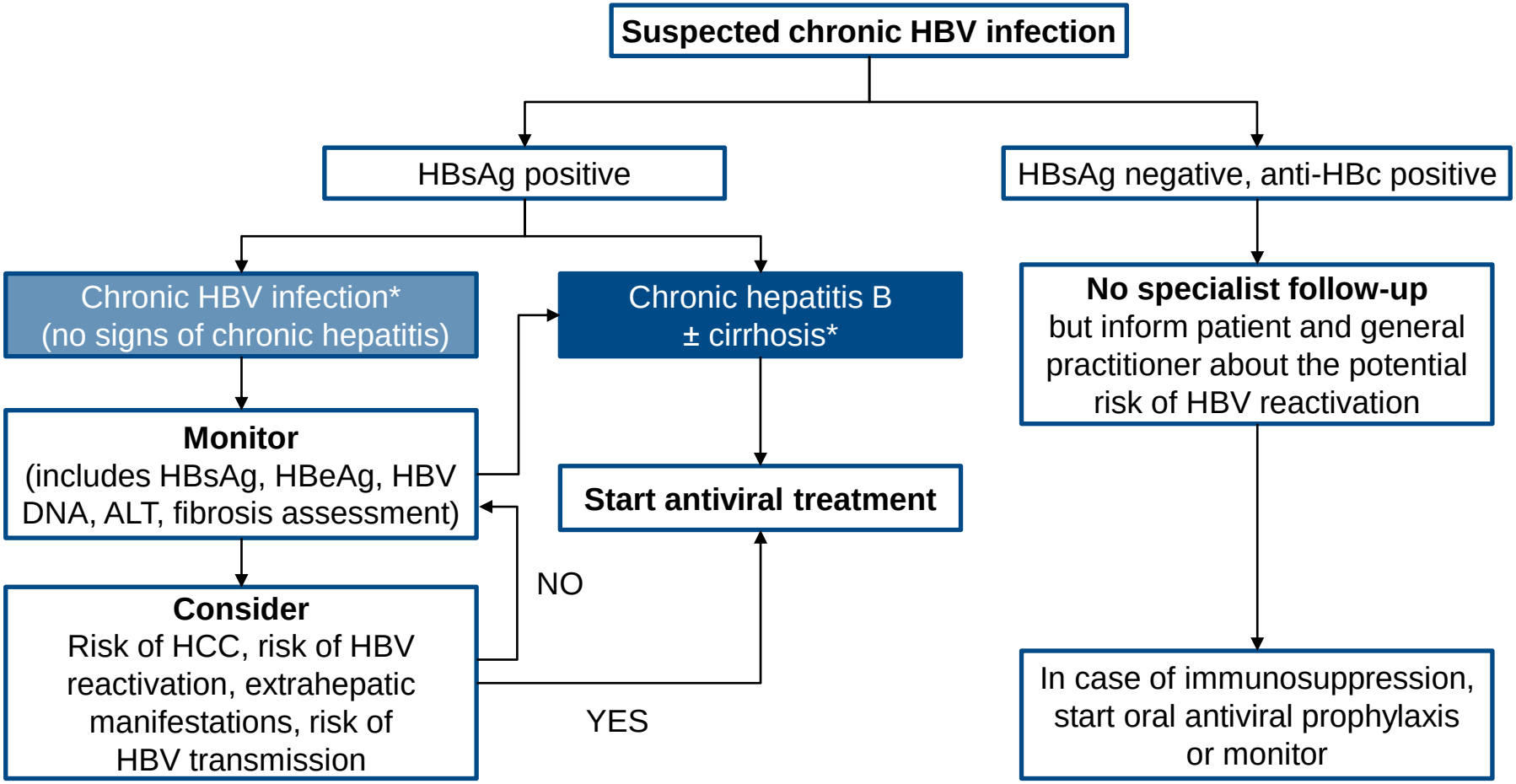
- Primarily based on the combination of 3 criteria
  - HBV DNA, serum ALT and severity of liver disease

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

EASL™ The Home of Hepatology

Algorithm for the management of chronic HBV infection



*See new nomenclature slide.

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

EASL™ The Home of Hepatology

Current treatment strategies for chronic hepatitis B: main concepts and features

Features	PegIFNα	ETV, TDF, TAF
Route of administration	Subcutaneous injections	Oral
Treatment duration	48 weeks	Long-term until HBsAg loss*
Tolerability	Low	High
Long-term safety concerns	Very rarely persistence of on-treatment AEs†	Probably not‡
Contraindications	Many§	None‖
Strategy	Induction of a long-term immune control	Inhibition of viral replication
Level of viral suppression	Moderate	Universally high
Effect on HBeAg loss	Moderate¶	Low in first year, moderate over long term
Effect on HBsAg levels	Variable¶	Low**
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	No	Minimal to none††

*Stopping NAs after some years might be considered in selected cases; †Psychiatric, neurological, endocrinological; ‡Uncertainties regarding kidney function, bone diseases for some NAs; §Decompensated disease, comorbidities etc.; ‖Dose adjustments in patients with eGFR <50 ml/min are required for all NAs except for TAF (no dose recommendation for TAF in patients with CrCl <15 ml/min who are not receiving haemodialysis); ¶Depending on baseline characteristics; **Slowly increases with treatment time in HBeAg-positive patients (a plateau in serological responses has been observed beyond treatment Year 4), usually very low in HBeAg-negative patients; ††So far no TDF or TAF resistance development has been detected

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

EASL™ The Home of Hepatology

Definitions of response to treatment

Responses	NA therapy	PegIFNα therapy
Virological (on-treatment)	**Response:** HBV DNA <10 IU/ml **Primary non-response:** <1 $\log_{10}$ decrease in HBV DNA after 3 months of therapy **Partial response:** HBV DNA decreased by >1 $\log_{10}$ but still detectable after ≥12 months of therapy in compliant patients **Breakthrough:** confirmed HBV DNA increase of >1 $\log_{10}$ above on-therapy nadir	**Response:** HBV DNA <2,000 IU/ml
Virological (off-treatment)	**Sustained response:** HBV DNA <2,000 IU/ml for ≥12 months after end of therapy	
Serological	HBeAg loss and development of anti-HBe* HBsAg loss and development of anti-HBs	
Biochemical	ALT normalization† (confirmed by ALT determination at least every 3 months for at least 1 year post-treatment)	
Histological	Decrease in necroinflammatory activity† without worsening in fibrosis compared with pre-treatment histological findings	

*Only for HBeAg-positive patients; †Based on traditional ULN (~40 IU/L);
†By ≥2 points in HAI or Ishak's system
EASL CPG HBV. J Hepatol 2017;67:370–98

EASL™ The Home of Hepatology

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™ The Home of Hepatology

Discontinuation of NA treatment

- Long-term therapy with NAs is usually required
  - HBV eradication is not usually achieved

Recommendations	Grade of evidence	Grade of recommendation
NAs <u>should</u> be discontinued • After confirmed HBsAg loss (± anti-HBs seroconversion)	II-2	1
NAs <u>can</u> be discontinued • In HBeAg-positive patients, without cirrhosis, who achieve stable HBeAg seroconversion and undetectable HBV DNA and complete ≥12 months of consolidation therapy **Close post-NA monitoring is warranted**	II-2	2
NAs <u>may</u> be discontinued • In selected HBeAg-negative patients, without cirrhosis, who achieve long-term (≥3 years) virological suppression, **if close post-NA monitoring can be guaranteed**	II-2	2

EASL™ The Home of Hepatology

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

CAN WE STOP NUCLEOS(T)IDE ANALOGUE THERAPY IN HBeAg-NEGATIVE CHRONIC HEPATITIS B PATIENTS?

© Can Stock Photo

EASL™
The Home of Hepatology

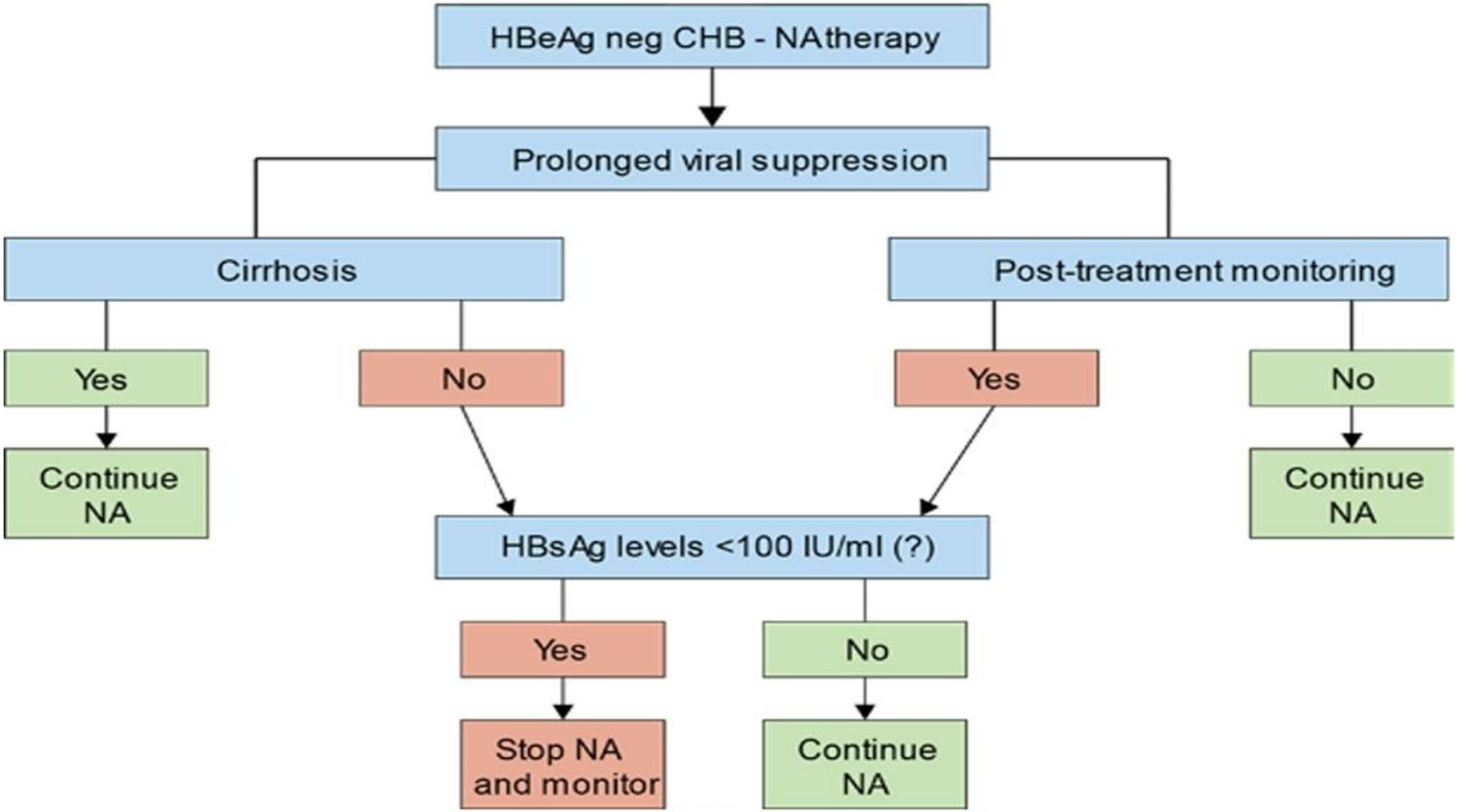
- Nucleos(t)ide analogue (NA) therapy may be stopped in non-cirrhotic, virally suppressed, HBeAg-negative chronic hepatitis B patients provided that post-treatment monitoring can be guaranteed.
- Virological remission and HBsAg loss can be observed in a good proportion of patients following NA discontinuation.
- Flares with liver decompensation may be observed in patients with cirrhosis.
- Low HBsAg levels at the end of treatment seem to be predictive of the off-treatment response and subsequent HBsAg loss.
- However, the predictive threshold for HBsAg is not yet established.
- Novel viral and immunological biomarkers are under evaluation to refine the decision algorithm.

Table 1. Summary of studies on off-therapy HBsAg seroclearance (modified from Jeng et al., Hepatology 2018, In press [8]).

Type of NA	N	LC	Non-LC	Male (%)	Age (yr)	Tx duration	FU duration	HBsAg loss	Incidence	HBsAg EOT*	Ref.
LAM	53	18	35	81	56	27 mo	47 mo	11/53	23% – 5 yrs	2 log IU/ml; reduction >1 log10	9
ADV	33	0	33	82	52	4-5 yrs	5.5 yrs	13/33	39% – 3 yrs	161 IU/ml	6
LAM	105	32	73	78	49	93 wks	49 mo		30% – 6 yrs	120 IU/ml	5
LAM, ADV, ETV, TDF	33	0	33	73	42	5.3 yrs	3 yrs	?			10
ETV, LAM, TLV	73	73	0	78	52	30 mo	66.8 mo	20/73	46% – 6 yrs	300 IU/ml	11
LAM, ETV	119	28	91	79	52	151 wks	6 yrs	44/119	55% – 6 yrs	50 IU/ml	12
TDF	21 (42)	0	21	79	45	>4 yrs	144 wks	4/21	19% 144 wks	<25,000 IU/ml	7
ETV, TDF, LAM, ADV, TLV	691	308	383	86	52	156 wks	155 wks	42/691	13% 6 yrs	<100 IU/ml	8

* values of HBsAg at EOT associated with subsequent HBsAg loss.

NA, nucleos(t)ide analogue; LAM, lamivudine; ADV, adefovir; ETV, entecavir; TDF, tenofovir disoproxil fumarate; TLV, telbivudine; Tx, treatment; FU, follow-up; EOT, end of treatment; Ref, reference; mo, months; wks, weeks; yrs, years.


HBeAg neg CHB - NAtherapy
Prolonged viral suppression
Cirrhosis
Post-treatment monitoring
Yes
No
Yes
No
Continue NA
Continue NA
HBsAg levels <100 IU/ml (?)
Yes
No
Stop NA and monitor
Continue NA

MANAGEMENT OF HBeAg-NEGATIVE PATIENTS WHO STOPPED LONG-TERM TREATMENT WITH NUCLEOS(T)IDE ANALOGUES

EASL™
The Home of Hepatology

- Discontinuation of nucleos(t)ide analogues (NA) frequently results in a virologic and biochemical flare that runs through different phases: the lag phase, reactivation phase, and consolidation phase.
- The flares observed during the reactivation phase are often transient and most likely represent a ~~trigger~~ for inducing a long-term HBV-specific immune control, and therefore do not need immediate interventions but close follow-up evaluations.
- In order to guarantee a safe and effective outcome of NA treatment discontinuation, the NA retreatment should be initiated timely enough to prevent harm for the patient, but virologic and biochemical flares should be tolerated to some extent to allow the establishment of an HBV-specific immune control.
- Recommendations are provided on how to follow and monitor patients during the different phases after NA cessation and when starting NA retreatment seems indicated.

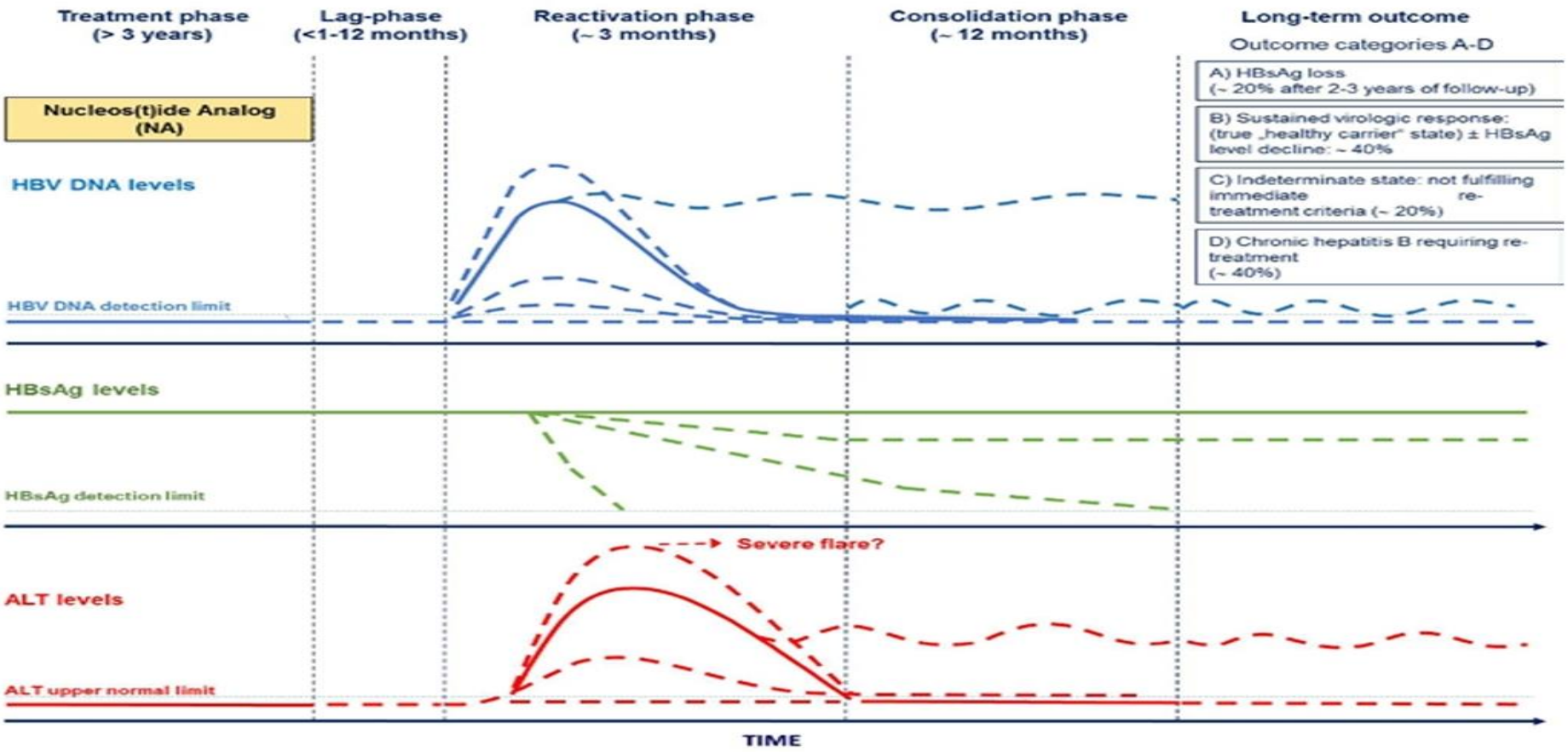


Fig. 1. Suggested phases after discontinuation of long-term NA treatment in patients with HBeAg-negative chronic hepatitis B according to courses of HBV DNA, HBsAg and ALT and possible long-term outcomes (modified according to Lampertico P and Berg T; Hepatology 2018, In press).

EASL™
The Home of Hepatology

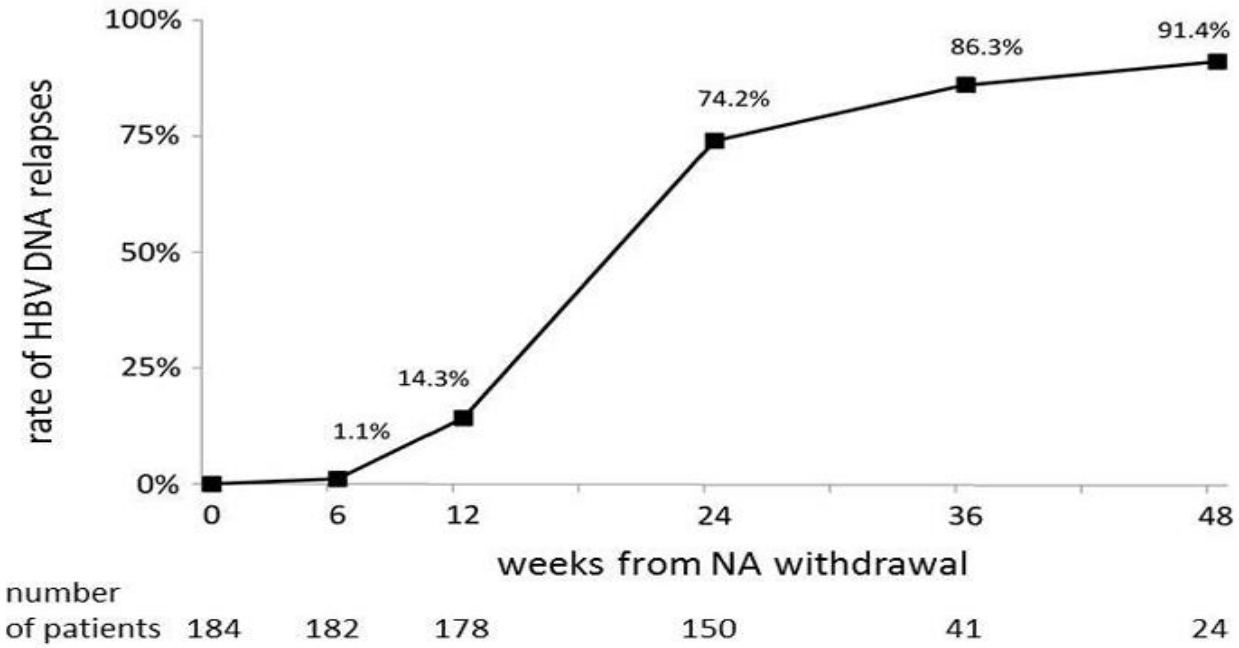


Fig. 2. Increase of HBV DNA relapses >2,000 IU/ml in HBeAg-negative patients after discontinuation of treatment with entecavir. Most virologic relapses occurred between weeks 12 and 24. At 48 weeks after NA discontinuation, a virologic relapse was seen in almost all patients (modified from Seto *et al.* [2]).

Table 1. Rates of virologic and biochemical relapses as well as the occurrence of hepatic decompensation and deaths associated with NA discontinuation in selected studies.

Study (first author)	n (cirrhosis)	Follow-up after NA disc. [range]	HBV DNA relapse (n [%])	ALT relapse (n [%])	Hepatic decompensation (n)	Death (n)
Jeng *et al.* [5]	691 (308)	155 weeks [2-614]	547 [79.2%]*	419 [60.6%]**	9 (all patients had cirrhosis at baseline)	3 (all patients with cirrhosis)
Kuo *et al.* [4]	401	48 weeks [48-350]	n.a.	274 [68.4%]	n.a.	1 (patient with cirrhosis)
Ha *et al.* [6]	145 (n.a.)	16 months [1–88]	95 [65.5%]*	93 [64%]¥	0	0
Seto *et al.* [2]	184 (34)	12 months	163 [91.4%]*	42 [26%]**	0	0
Papatheodoridis *et al.* [3]	130 (0)	24 months	108 [83%]*	55 [42%]**	0	0
Berg *et al.* [8]	21 (0)	144 weeks	21 [100%]∑	7 [33%]** at week 12	0	0

* Increase of HBV DNA >2,000 IU/ml; ** Increase of ALT >2x ULN; ∑ any increase in HBV DNA; ¥ any ALT increase.

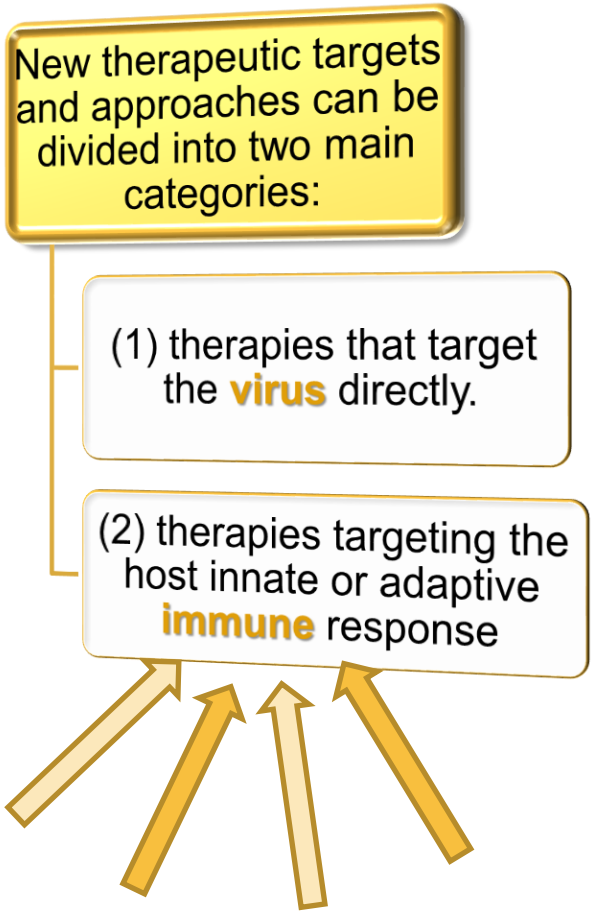
EASL™
The Home of Hepatology

Table 2. Proposed retreatment criteria for non-cirrhotic HBeAg-negative patients after NA discontinuation (modified from Berg T et al. [8]).

1.	Confirmed (*i.e.*, two consecutive central laboratory results) increase in direct bilirubin from baseline, and ALT ULN at the confirmatory test
2.	Confirmed sustained increase in prothrombin time ≥2.0 s from baseline with appropriate vitamin K levels and elevated ALT
3.	Confirmed elevated ALT 10 x ULN with or without associated symptoms
4.	ALT 2 x ULN and ≤5x ULN persisting for ≥84 days (12 weeks) as well as a HBV DNA relapse ≥ 20,000 copies/ml
5.	ALT 5 x ULN and ≤10 x ULN persisting for ≥28 days (4 weeks)

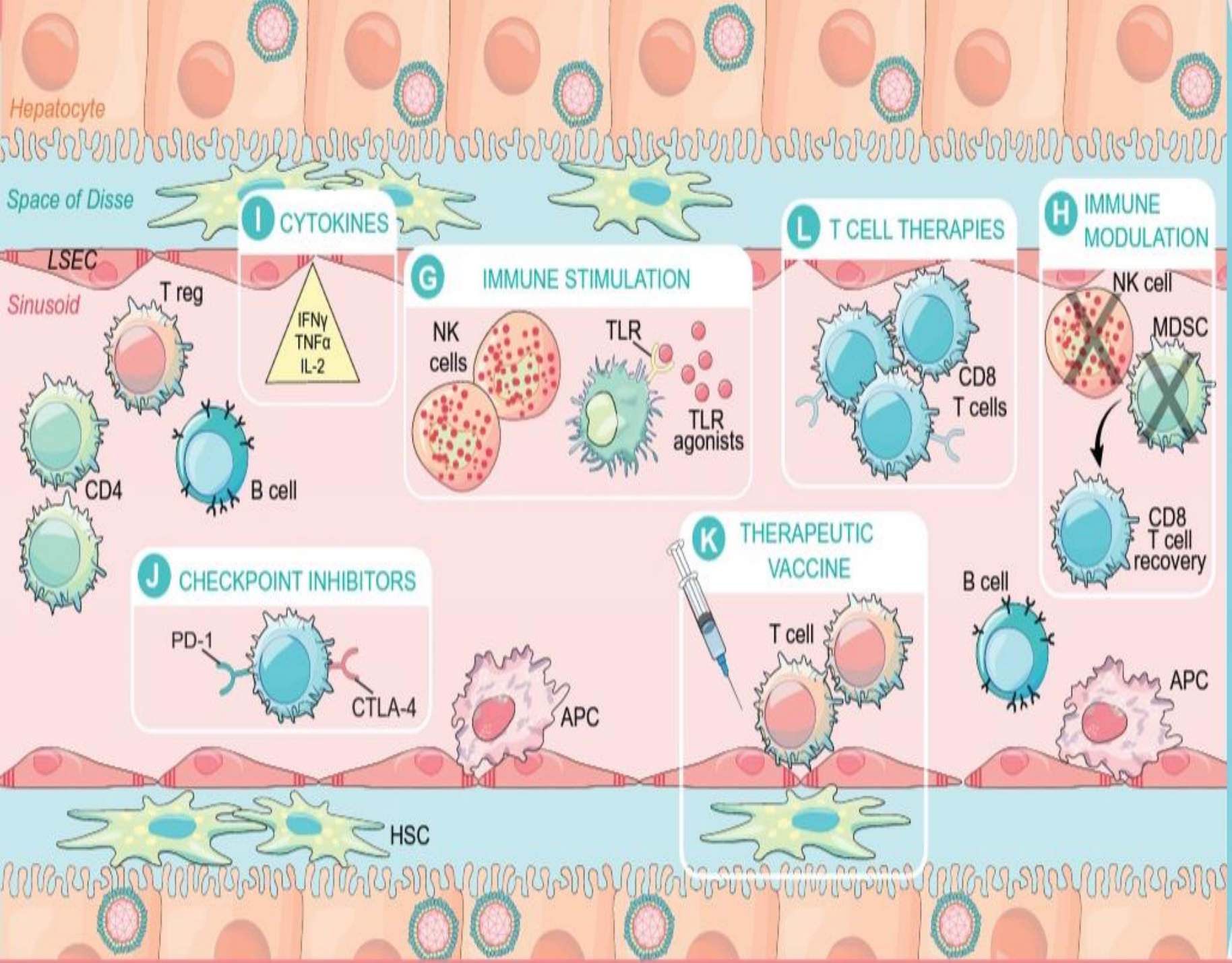
The Future of HBV

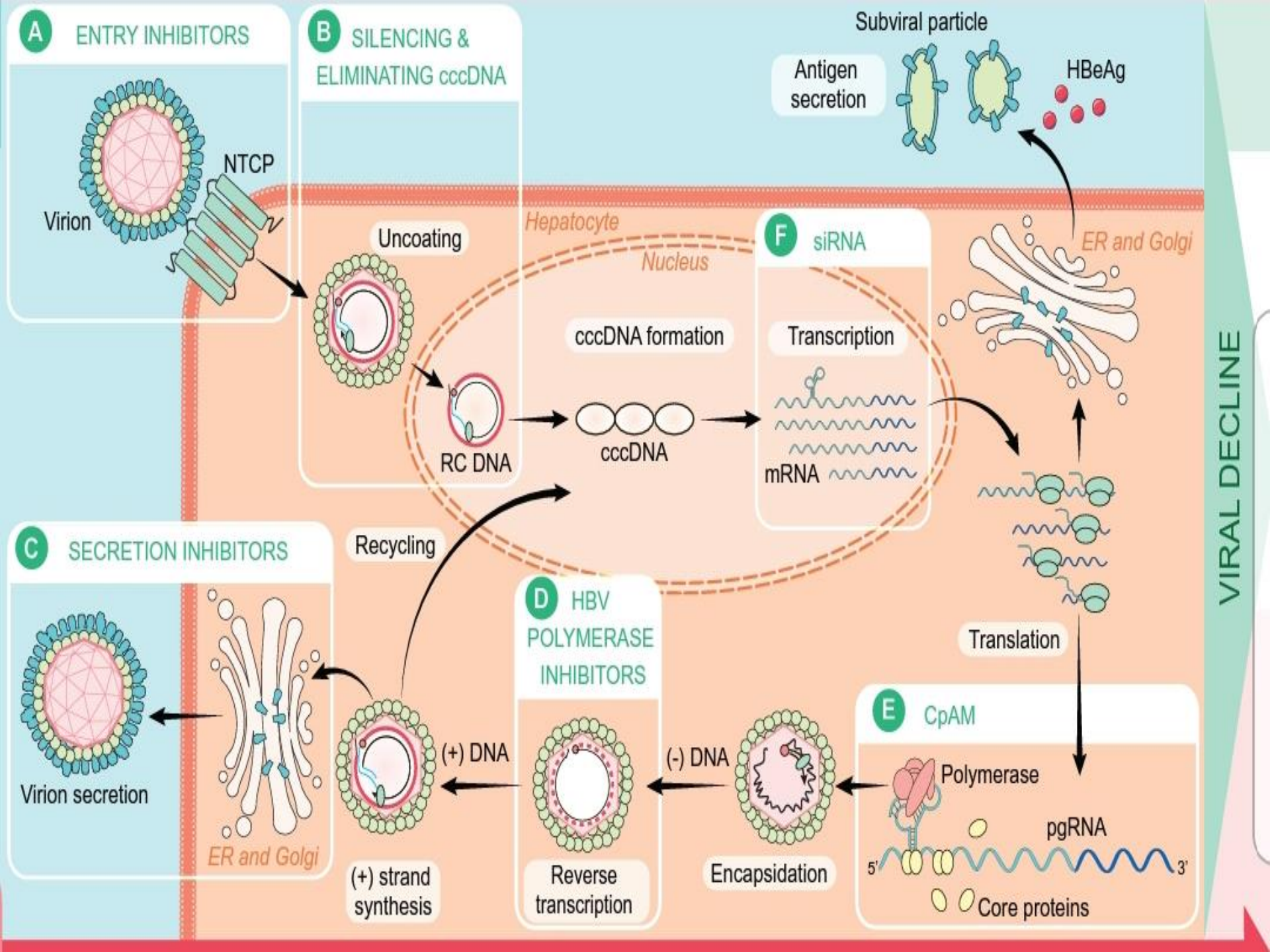
Cure?



Functional therapy ??

EASL™
The Home of Hepatology


Hepatocyte
Space of Disse
LSEC
Sinusoid
I CYTOKINES
IFNγ
TNFα
IL-2
G IMMUNE STIMULATION
NK cells
TLR
TLR agonists
L T CELL THERAPIES
CD8 T cells
H IMMUNE MODULATION
NK cell
MDSC
CD8 T cell recovery
T reg
CD4
B cell
J CHECKPOINT INHIBITORS
PD-1
CTLA-4
APC
K THERAPEUTIC VACCINE
T cell
B cell
APC
HSC
IMMUNE RECOVERY


A ENTRY INHIBITORS
Virion
NTCP
B SILENCING & ELIMINATING cccDNA
Uncoating
RC DNA
Hepatocyte
Nucleus
cccDNA formation
cccDNA
F siRNA
Transcription
mRNA
Subviral particle
Antigen secretion
HBeAg
ER and Golgi
Translation
VIRAL DECLINE
C SECRETION INHIBITORS
Virion secretion
ER and Golgi
Recycling
D HBV POLYMERASE INHIBITORS
(+) DNA
(+) strand synthesis
Reverse transcription
(-) DNA
Encapsidation
E CpAM
Polymerase
pgRNA
5'
3'
Core proteins

PS-027

Preclinical antiviral drug combination studies utilizing novel orally bioavailable investigational agents for chronic hepatitis B infection: AB-506, a next generation HBV capsid inhibitor, and AB-452, a HBV RNA destabilizer

Nagraj Mani1, Alice H.L.LI2, Andrzej Ardzinski1, Laurèn Bailey1, Janet R. Phelps2, Robbin Burns2, Tim Chiu2, Andrew G. Cole1, Andrea Cuconati1, Bruce D. Dorsey1, Ellen Evangelista2, Dimitar Gotchev1, Troy O. Harasym2, Agnes Jarosz2, Salam Kadhim2, Andrew Kondratowicz2, Steven G. Kultgen1, Kaylyn Kwak2, Amy C.H Lee2, Sara Majeski2, Kevin Mcclintock2, Joanna Pan2, Chris Pasetka2, Rene Rijnbrand1, Alexander Shapiro2, Holly M. Steuer1, Kim Stever1, Sunny Tang2, Xiaowei Teng2, Melody Wong2, Michael J. Sofia1

1Arbutus Biopharma Inc., Warminster, PA, United States; 2Arbutus Biopharma Inc., Burnaby, BC, Canada

Email: nmani@arbutusbio.com

Background and Aims: Chronic hepatitis B infection affects ~240 million people worldwide who are at risk of developing cirrhosis, liver failure, and hepatocellular carcinoma and, unfortunately, currently approved therapies have poor cure rates. Increasing cure rates will require a combination regimen that blocks viral replication, reduces antigen load, attenuates cccDNA formation, and activates host immune responses to control residual virus. We evaluated the anti-HBV activities of two novel orally administered agents, a HBV capsid inhibitor AB-506 and a HBV RNA destabilizer AB-452, in combination with approved nucleos(t)ide analogs (NA), entecavir (ETV), tenofovir disproxil fumarate (TDF), tenofovir alafenamide (TAF), as well as the investigational RNA interference agent, ARB-1467.

Methods: ***In vitro combination studies were conducted using three-dimensional modeling for antiviral*** drug-drug interactions (Prichard and Shipman1990) by measuring the reduction of rcDNA and HBsAg levels in HBV cell culture systems. Results were analyzed using MacSynergy II software to determine if a combination was additive, synergistic, or antagonistic. Cell viability was assessed using the CellTiter-Glo® reagent. *In vivo antiviral activities were studied in a hydrodynamic injection (HDI) HBV* mouse model. HBV markers were measured using bDNA, qPCR and ELISA assays.

Results: The ***in vitro dual combinations of AB-506 or AB-452 with approved NAs or ARB-1467 ranged*** from additive to moderately synergistic at reducing HBV rcDNA and HBsAg levels with no significant effects on cell viability. After a once-daily 7-day oral treatment period in HDI HBV mice, dual combinations of AB-506+AB-452, AB-506+TDF, and AB-452+TDF demonstrated a strong antiviral activity with mean 1.4, 1.9, and 2.2 log reductions in serum HBV DNA *vs the vehicle control,* respectively, whereas the triple combination effected larger serum HBV DNA reductions, 2.8 log *vs the* vehicle control. All AB-506 and AB-452 treated groups demonstrated reductions in liver HBV DNA, with negligible reduction observed with TDF alone. Serum HBsAg reduction was detected in AB-452 treated groups, and when combined with AB-506 and/or TDF there was no adverse effect on the ability of AB-452 to reduce HBsAg.

Conclusion: These preclinical investigations suggest that these agents when combined have distinct but mechanistically compatible *in vitro and in vivo antiviral activities and may feasibly be used in future* combination therapeutic regimens.

PS-028

Combination treatment of a TLR7 agonist RO7020531and a capsid assembly modulator RO7049389 achieved sustainable viral loadsuppression and HBsAg loss in an AAV-HBV mouse model

Lue Dai1, Youjun Yu2, Lili Gu1, Jie Zhao1, Lina Zhu1, Hongying Yun1, Ying Ji1, Wei Zhu1, John Young3, Lu Gao1

1Roche Innovation Center Shanghai, Shanghai, China; 2Roche Innovation Center Shanghai; 3Roche Innovation Center Basel

Email: lu.gao@roche.com

Background and Aims: The ideal endpoint of therapy for CHB patients is sustained viral suppression as evidenced by the loss of HBsAg with or without anti-HBs seroconversion. With existing HBV therapies (Peg IFN, nucleos(t)ides), HBsAg loss only occurs in approximately 3% of patients after 1 year of treatment. Here we evaluated the oral combination of two novel clinical Phase I molecules, a TLR7 agonist RO7020531 and a capsid assembly modulator RO7049389, in the AAV-HBV mouse model.

Method: In vivo efficacy of compounds was studied in a mouse model with a recombinant adeno associated virus carrying hepatitis B virus genome (AAV-HBV) for 6 weeks followed by a 6-week offtreatment period. The levels of HBV DNA, HBsAg, and HBeAg in mouse serum were measured by quantitative polymerase chain reaction (qPCR), HBsAg chemiluminescent immunoassay (CLIA), HBeAg CLIA kits, and a mouse IgG ELISA development kit, respectively. Germinal center B cell population in the spleen was analyzed by FACS analysis.

Results: In an AAV-HBV model, oral administration of the TLR7 agonist RO7020531 significantly reduced both HBV DNA and HBsAg levels with gradual rebound in these markers during a follow-up off-treatment period. Combining this TLR7 agonist with the approved nucleoside analog entecavir did not lead to greater HBsAg reduction. In striking contrast, however, the combination of RO7020531 and the capsid assembly modulator RO7049389, led to a dramatic reduction of HBsAg and HBV DNA with the levels declining to at or below the lower limit of quantification. Most importantly, during the offtreatment period, the effect on HBsAg was sustained, whereas HBV DNA rebound was minimum. Emergence of high levels of anti-HBs antibodies was also observed in a number of mice during the offtreatment period. The combination therapy of TLR7 agonist and capsid assembly modulator was also associated with upregulated germinal center B cells in the spleen and increased level of anti-HBs antibody in the serum. In addition, HBeAg level in the combination group was reduced by more than 1-log, and similar to that in the monotherapy group of capsid assembly modulator.

Conclusion: In the AAV-HBV mouse model, the combination of the TLR7 agonist RO7020531 and the capsid assembly modulator RO7049389 demonstrated robust suppression of both HBsAg and HBV DNA levels and with the additional emergence of anti-HBs antibodies in several animals. These data highlight the merits of exploring this combination in the clinic as a potential means to achieve a functional cure for CHB infection.

GS-005

Final results of a multicenter, open-label phase 2b clinical trial to assess safety and efficacy of

Myrcludex B in combination with Tenofovir in patients with chronic HBV/HDV co-infection

Heiner Wedemeyer1, Pavel Bogomolov2, Antje Blank3 4, Lena Allweiss5 6, Maura Dandri-Petersen5 6, Birgit Bremer1, Natalia Voronkova2, Katrin Schöneweis4 7, Anita Pathil8, Jürgen Burhenne3 4, Mathias Haag9 10, Matthias Schwab9 10, Walter-Emil Haefeli3 4, Julian Schulze Zur Wiesch6 11, Alexander Alexandrov12, Stephan Urban4 13

1Hannover Medical School, Department of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; 2Moscow Regional Research Clinical Institute, Hepatology Department, Moscow, Russian Federation; 3Heidelberg University Hospital, Department of clinical Pharmacology and Pharmacoepidemiology, Heidelberg, Germany; 4German Center for Infection Research (DZIF), Heidelberg Partner Site, Heidelberg, Germany; 5University Medical Center Hamburg-Eppendorf, I. Department of Internal medicine, Hamburg, Germany; 6German Center for Infection Research (DZIF), Lübeck-Borstel Partner site, Hamburg, Germany; 7University Hospital Heidelberg, Department of Infectious Diseases, Molecular Virology, Heidelberg, Germany; 8Heidelberg University Hospital, Internal Medicine IV, Gastroenterology and Hepatology, Heidelberg, Germany; 9IKP Stuttgart, Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology , Germany; 10German Center for Infection Research (DZIF), Tübingen Partner Site; 11University Medical Center Hamburg-Eppendorf, Department of Internal Medicine, Infectious Diseases Unit, Hamburg, Germany; 12MYR GmbH, Bad Homburg , Germany; 7University Hospital Heidelberg, Department of Infectious Diseases, Molecular Virology, Heidelberg, Germany

Email: Katrin.Schoeneweis@med.uni-heidelberg.de

Background and Aims: Currently there is no approved drug for hepatitis D virus (HDV) infection. Myrcludex B (MyrB) is a first-in-class entry inhibitor blocking the HBV/HDV receptor NTCP. We previously reported end-of-treatment data of a Phase 2 clinical trial in chronic HDV infection (Wedemeyer et al.; Hepatology 2017, DOI: 10.1002/hep.29500). Here we present follow up data after stopping MyrB therapy.

Methods: 120 patients with chronic Hepatitis D were randomized in four treatment arms. Treatment with TDF 245mg/day started not less than 12w prior to MyrB. MyrB was administered s.c. once daily at 2 (A), 5 (B) or 10mg (C) for 24w followed by a 24w period continuing TDF. Patients in arm D received TDF alone. The primary endpoint was HDV RNA reduction by 2log or negativity.

Results: At abstract submission, virology data from 41 patients who completed the week 12 of follow up, and ALT data from 94 patients are available. **Safety: MyrB was very well tolerated. Apart from bile** acids increase, no specific AE pattern could be identified for MyrB. After MyrB cessation, two hepatitis exacerbations after stopping MyrB were reported as SAEs. The ALT flairs were not associated with bilirubin increases and resolved without intervention. Bile acid levels returned to baseline at the follow up week 1. **Efficacy: At end of treatment, the primary endpoint was reached by 46.4%, 46.8%, 76.6%,** and 3.3% of patients of arms A, B, C, and D. Median HDV RNA declined by -1.75log, -1.60log, -2.70log and -0.18log. Plasma HDV RNA decline correlated with intrahepatic decrease of HDV RNA replication. ALT normalization was achieved in 42.8%, 50%, 40% and 6.6%. Mean liver stiffness values significantly declined in all MyrB groups from baseline to treatment week 24 but not in the control group.

At follow up week 12, an HDV RNA relapse occurred in 60%, 80% and 83% of HDV RNA responders. Median HDV RNA increased by 1.26log, 0.62log, 1.85log, 0log in arms A, B, and C and D. HDV RNA levels remained -0.77log, -1.27lo, -0.99log, and 0log below BL levels. Median ALT increased from 44.0U/l, 40.5U/l, 43.0U/l and 76.0U/l to 79U/l, 63U/l, 93U/l and 64U/l.

Conclusion: Myrcludex B shows a dose-dependent antiviral efficacy against HDV associated with improvements of biochemical activity and liver stiffness. Sustained HDV control after 24 weeks of therapy is possible in single patients but longer treatment durations or even maintenance therapy need to be investigated in future trials.


Syrian


WE'RE DONE EXPLAINING
THANKS FOR LISTENING :)