HBV
Nuovi marcatori e target terapeutici

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Outline

- Overview Hepatitis B Virus
  - Definitions
  - Current treatment options
- New biomarkers for HBV
  - Clinical implication & relevance
- New anti-HBV strategies

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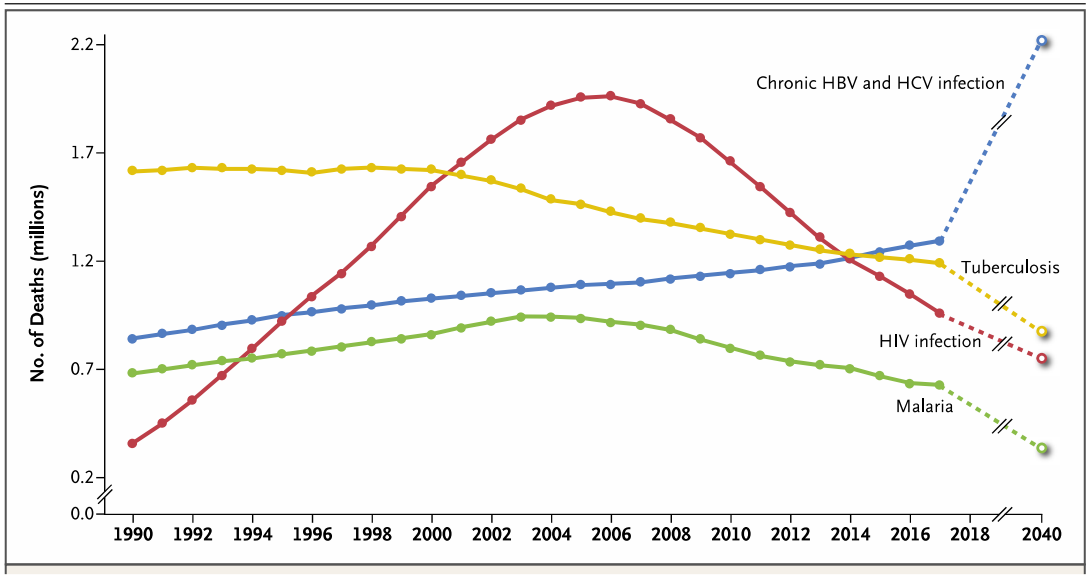
Overview Hepatitis B Virus

Chronic hepatitis B (CHB) is a major global health challenge



Urgent need →develop curative therapies

Thomas, D. L. N. Engl. J. Med. 2020

Definition of HBV Cure

Complete cure

the permanent elimination of all HBV forms, including the HBV transcriptional template (cccDNA)

Functional cure

the loss of detectable serum hepatitis B surface antigen (HBsAg) with or without seroconversion to anti-HBs antibody

Current treatment options

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

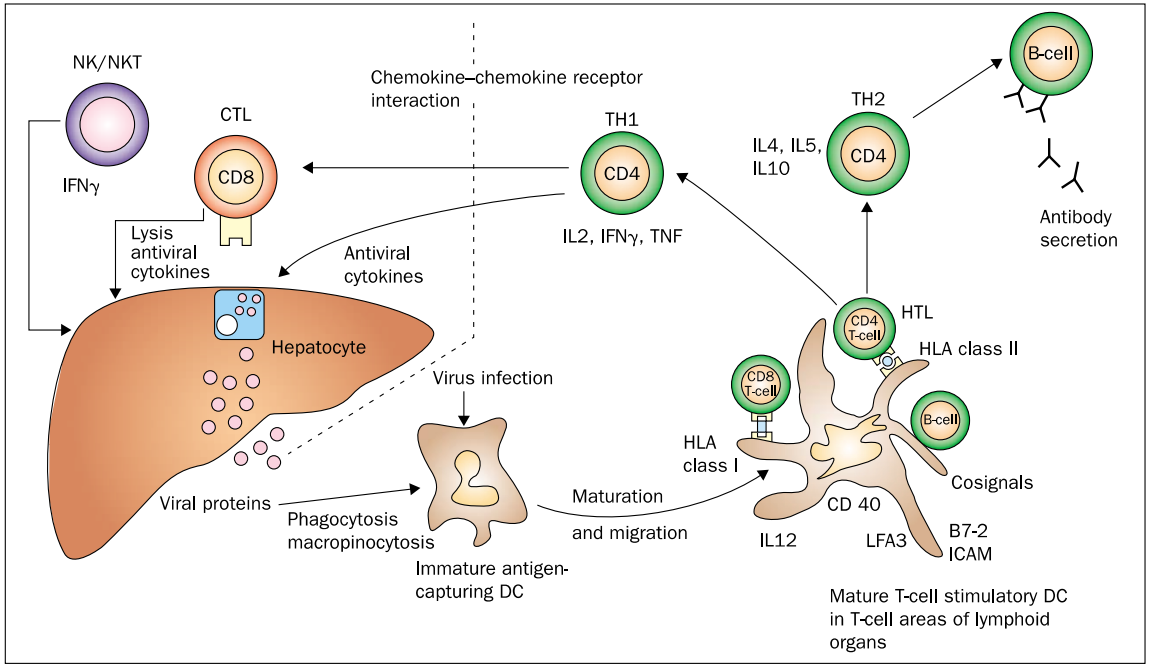
EASL CPG HBV. J Hepatol 2017;67:370–98

EASL The Home of Hepatology

Immunobiology and pathogenesis

HBV is a non-cytopathic DNA virus

→ host immune response mediates both virus control and liver disease



Jung MC et al. Lancet Infect Dis. 2002

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Nucleoside Analogue Withdrawal

- 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

pts without any evidence of cirrhosis

Definition of HBV Cure

Complete cure

the permanent elimination of all HBV forms, including the HBV transcriptional template (cccDNA)

Functional cure

the loss of detectable serum hepatitis B surface antigen (HBsAg) with or without seroconversion to anti-HBs antibody

Partial cure

sustained low or undetectable HBV DNA level with HBsAg positive after a finite course of treatment

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Unmet clinical need

anti-HBV treatments inhibit HBV replication BUT they cannot completely eliminate HBV from hepatic cells

HBV persistence

HBV reactivation
disease progression

Outline

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Unmet clinical need

anti-HBV treatments inhibit HBV replication BUT they cannot completely eliminate HBV from hepatic cells

→ helpful to identify treatment response before or early during treatment

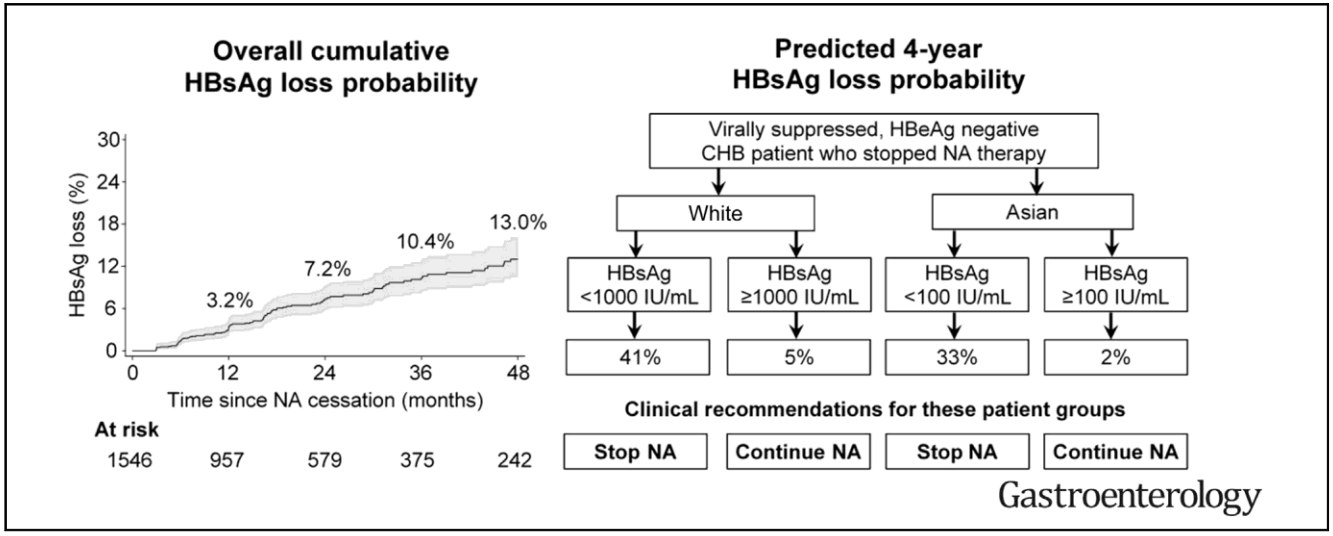
↓

HBV persistence
HBV reactivation
disease progression

→ ability to stratify by disease stages and risk for complications

quantitative HBsAg

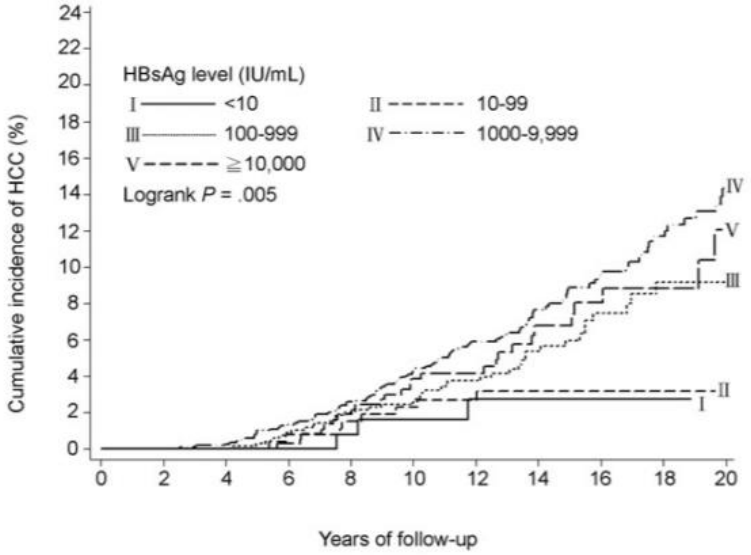
Low HBsAg (<10-100) best predictor in prevention of relapse after stopping NA



Hirode, Gastroenterology 2022

quantitative HBsAg

Higher HBsAg levels independently associated with HCC development



Number at risk

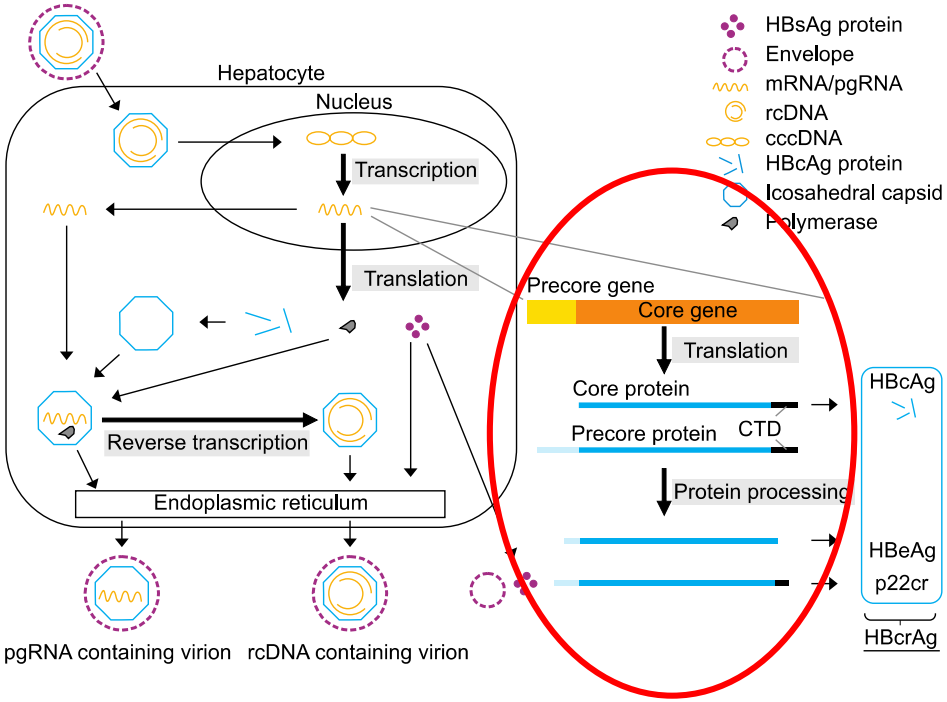
Serum HBsAg level at baseline (IU/mL)											
<10	129	129	129	129	126	113	85	56	21	9	7
10-99	268	268	268	265	262	248	192	128	76	54	37
100-999	703	703	703	697	684	631	484	353	220	135	92
1000-9999	1215	1215	1212	1198	1175	1080	868	603	400	281	196
≧10000	373	373	373	372	363	329	263	184	119	74	50

Tseng et al., *Gastroenterology* 2012

HB core related antigen (HBcrAg)

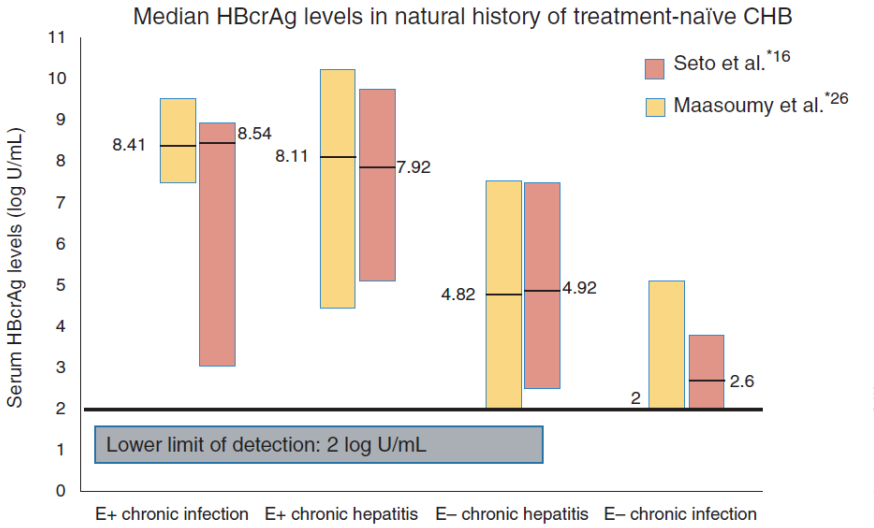
→ measures a composite of HBeAg, HBcAg, and p22cr protein

→ marker of intrahepatic HBV cccDNA and its transcriptional activity.



Mak LY, et al: Gut and Liver, 2019

HBcrAg : clinical relevance



HBcrAg levels higher in HBeAg-positive vs negative phase

Mak et al., Aliment Pharmacol Ther 2018

Useful in the evaluation of new antiviral therapies aiming at a functional cure of HBV infection either by targeting directly or indirectly the intrahepatic cccDNA pool

Useful biomarker to predict relapse following treatment cessation

Mak et al: Gut and Liver, 2019

HBcrAg : clinical relevance

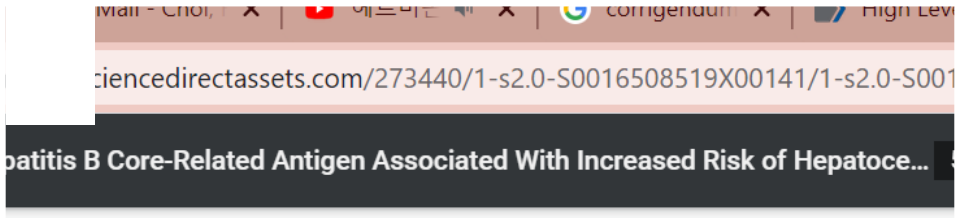
Pregenomic HBV RNA and Hepatitis B Core-Related Antigen Predict Outcomes in Hepatitis B e Antigen–Negative Chronic Hepatitis B Patients Suppressed on Nucleos(T)ide Analogue Therapy

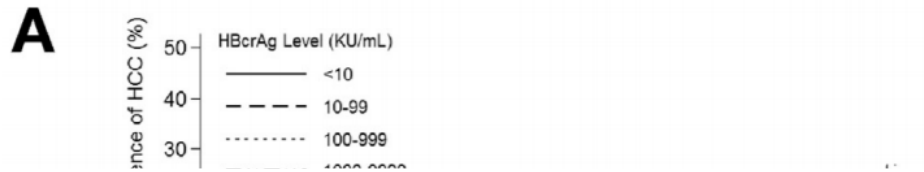
Table 3 - Clinical Characteristics of Cohort B at Time of NA Withdrawal (n = 23)

	All Cohorts (n = 23)	No Flare (n = 9)	Mild Flare (n = 10)	Severe Flare (n = 4)
Male patients (n, %)	n = 14 (61)	n = 4 (44)	n = 6 (60)	n = 4 (100)
Median FibroScan stiffness (IQR; range)	4.7 kPa (2.3; 2.9-8.1)	4.6 kPa (0.6; 3.3-7.8)	5.7 kPa (2.5; 2.9-8.1)	4.9 kPa (3.0; 4.2-7.9)
HBeAg positive (n, %)	N = 0 (0)	N = 0 (0)	N = 0 (0)	N = 0 (0)
Median HBV DNA at time of withdrawal (IQR; range)	0 log_{10}IU/mL (0; 0)	0 log_{10}IU/mL (0; 0)	0 log_{10}IU/mL (0; 0)	0 log_{10}IU/mL (0; 0)
Median HBsAg at time of withdrawal (IQR; range)	3.41 log_{10}IU/mL (1.0; 2.4-4.5)	3.53 log_{10}IU/mL (1.2; 2.4-4.4)	3.28 log_{10}IU/mL (0.7; 3.1-4.4)	3.51 log_{10}IU/mL (0.9; 3.4-4.5)
Median HBcrAg at time of withdrawal (IQR; range)**	2.0 log_{10}U/mL (0; 2.0-5.4)	2.0 log_{10}U/mL (0; 2.0)	2.0 log_{10}U/mL (0; 2.0)	4.2 log_{10}U/mL (0.9; 3.1-5.4)
Median pg HBV RNA at withdrawal (IQR; range)**	0 log_{10}U/mL (0; 0.0-2.2)	0 log_{10}U/mL (0; 0)	0 log_{10}U/mL (0; 0)	1.93 log_{10}U/mL (0.8; 0.0-2.2)
Median ALT activity at time of withdrawal (IQR; range)	24 IU/L (19; 15-53)	24 IU/L (11; 18-42)	26 IU/L (18; 15-53)	22 IU/L (22; 17-52)
Proportion of HBcrAg not detected at NA stop (<3 log_{10}U/mL), n (%)	n = 19 (83)	n = 9 (100)	n = 10 (100)	n = 0 (0)
Proportion of pg HBV RNA not detected at NA stop (1.65 log_{10}U/mL), n (%)	n = 20 (87)	n = 9 (100)	n = 10 (100)	n = 1 (25)
Duration of therapy at time of withdrawal (IQR; range)	77 months (53; 38-118)	55 months (42; 38-114)	92 months (41; 58-118)	66 months (44; 54-110)

Carey I. Hepatology 2020

HBcrAg : clinical relevance



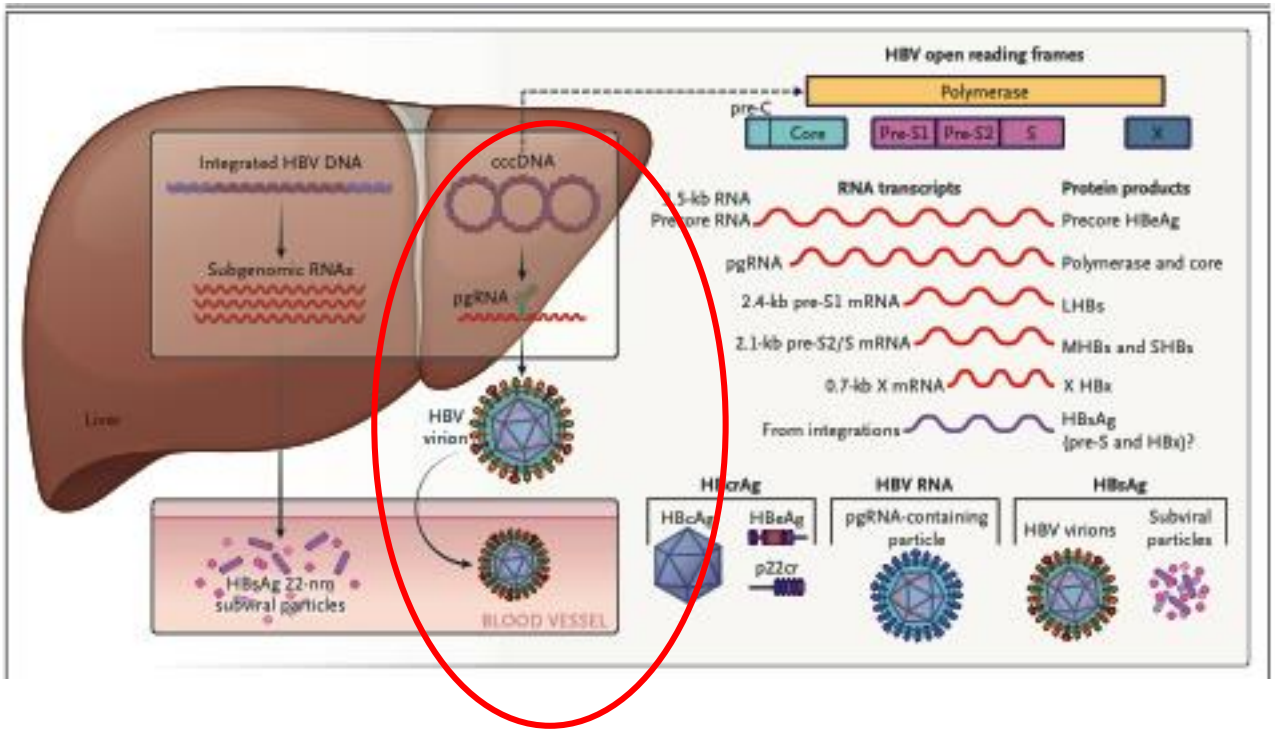


Tseng et al., Gastroenterology 2019

Higher serum HBcrAg was shown to be associated with HCC development in both treatment-naïve and treatment experienced patients

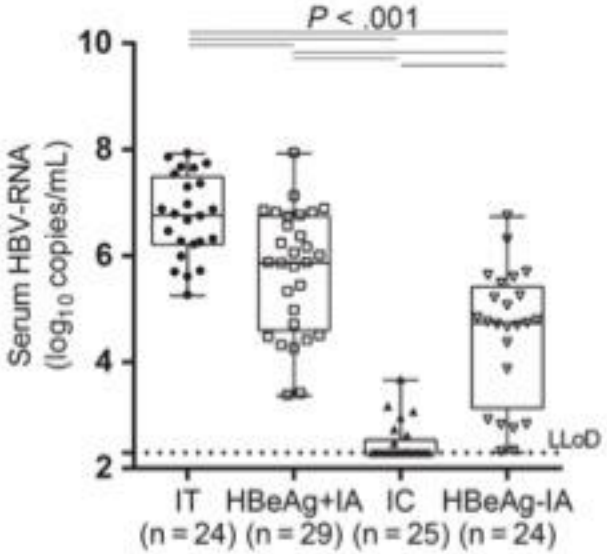
serum HBV RNA

Biomarker measures the number of virions containing pre-genomic RNA (pgRNA) which reflects the ongoing transcriptional activity of cccDNA



Mak LY, et al: Gut and Liver, 2019

serum HBV RNA : clinical relevance



The highest levels were observed in HBeAg-positive HBeAg-positive vs negative phase

Wang et al., Journal of Viral Hepatitis. 2018

Useful in the evaluation of new antiviral therapies aiming at a functional cure of HBV infection either by targeting directly or indirectly the intrahepatic cccDNA pool

Useful to predict durable response after stopping NA: undetectable HBVRNA together with HBsAg<10

serum HBV RNA : clinical relevance

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Carey I. Hepatology 2020

Clinical application & relevance

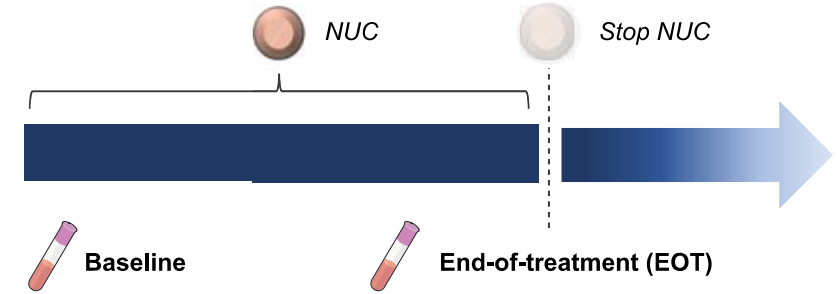
Table 2. Potential Clinical Application of HBcrAg and HBV RNA in Chronic Hepatitis B Infection

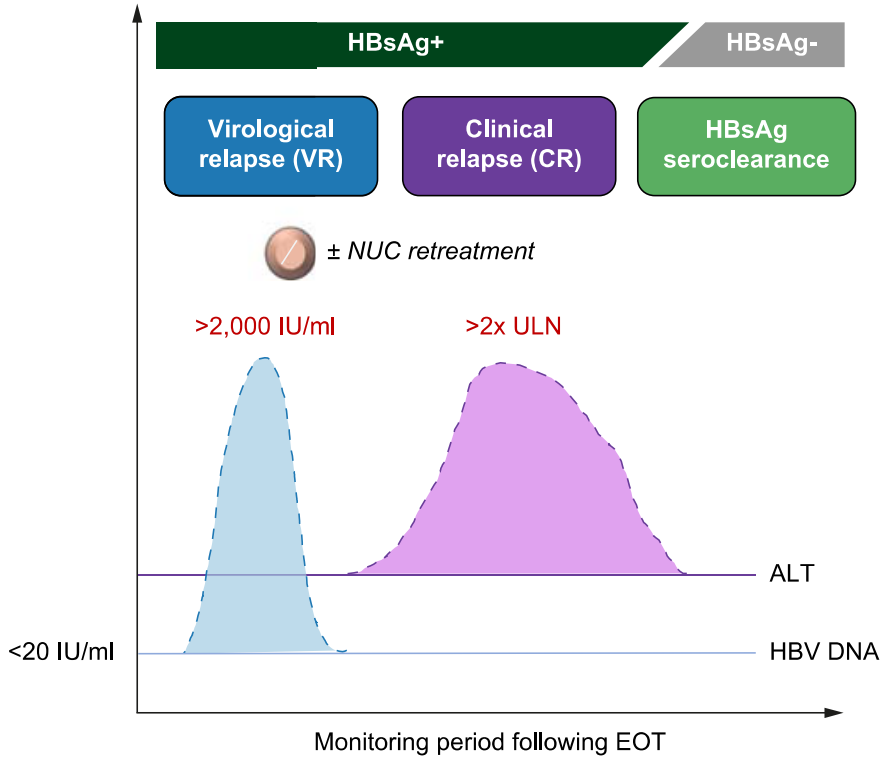
Area of interest	HBcrAg	HBV RNA
Natural history		
Differentiate disease phases	+	+
Predicts spontaneous HBeAg seroconversion	+	No data
Predicts spontaneous HBsAg seroclearance	(–)*	No data
Antiviral treatment: PEG-IFN or NA		
Predict treatment-induced HBeAg seroconversion	+	+
Predict post-NA cessation 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	(–)†

Mak et al: Gut and Liver, 2019

Utility of novel viral and immune markers in predicting HBV treatment endpoints: A systematic review of treatment discontinuation studies

A systematic review of 33 studies comprising of 2,986 unique subjects with chronic hepatitis B infection who discontinued nucleoside analogue (NUC)





References:
1: Xie Y 2021, Kuo YH 2021, Liu Y 2020
2: Fan R 2020A, Fan R 2020B, Xia M 2021
3: Fan R 2020B, Liao G 2021, Xie Y 2021, Huang PY 2021, Tseng TN 2020
4: Chi H 2019

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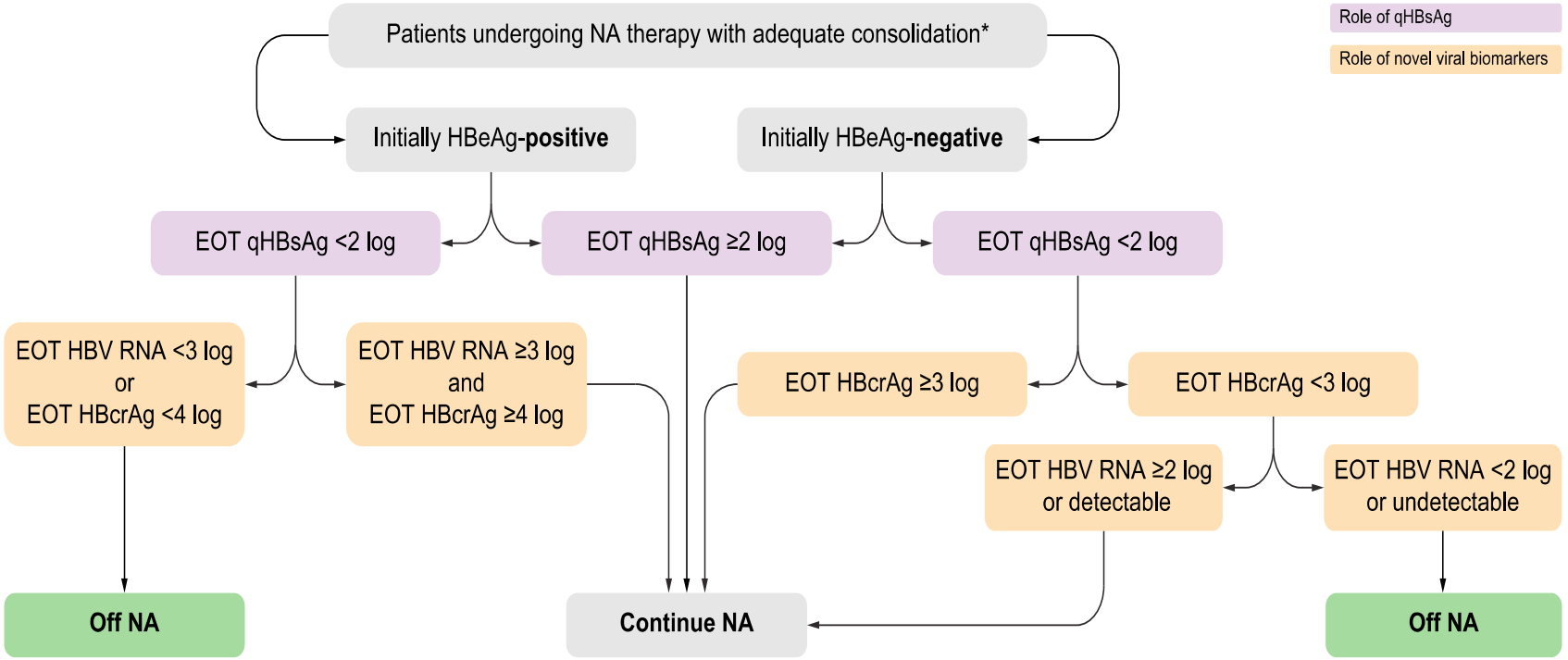
JHEP|Reports



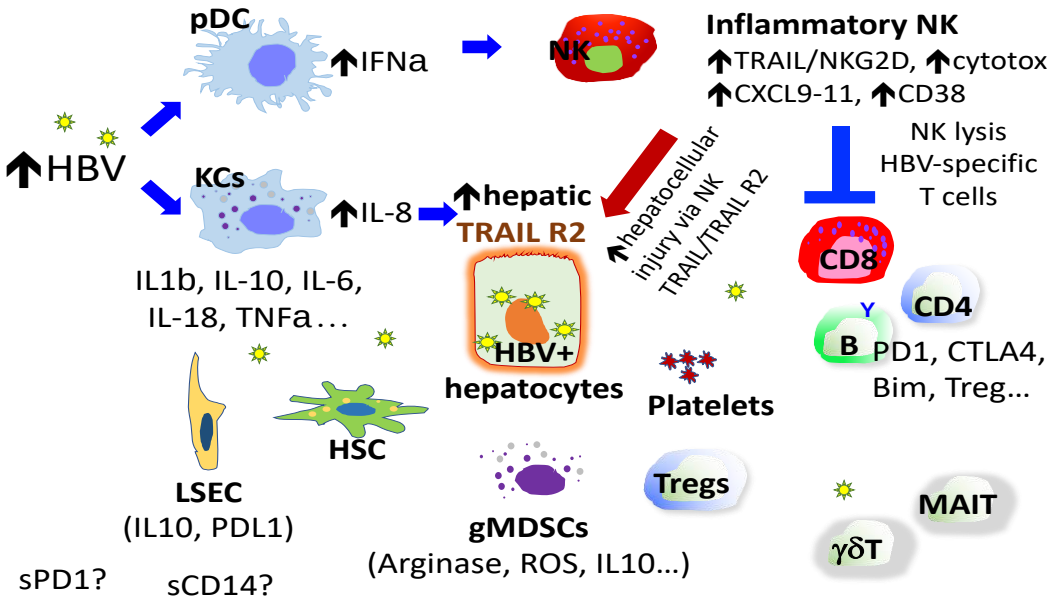
Proposed algorithm to decide whether NA should be discontinued based on qHBsAg, HBcrAg, and HBV RNA stratified by HBeAg status.

Immunological serum biomarkers

Immune exhaustion concept

→ HBV persistence is associated with global and virus-specific adaptive immune dysregulation or tolerance.

Kramvis A, Nat Rev Gastroenterol Hepatol. 2022
Mak LY, et al: Gut and Liver, 2019



ICE-HBV International Coalition to Eliminate HBV

Immunological serum biomarkers : clinical relevance

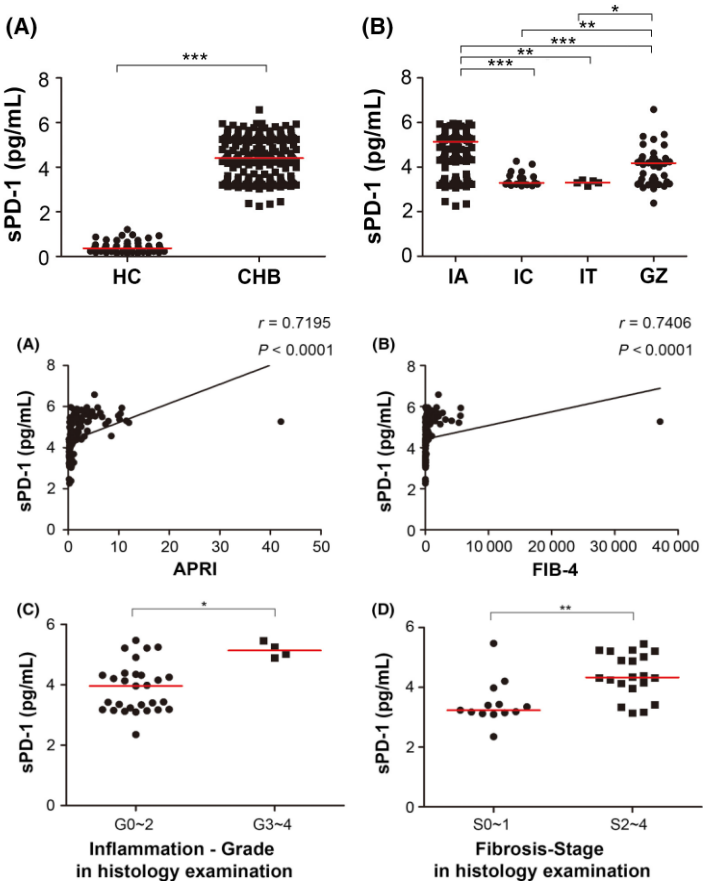
In CHB clinical course

- IFNa, IL-8 -> NK activation
- IP-10/CXCL10
- CXCL9/10/11
- IDO
- Arginase
- sPD-1

sPD-1:
soluble programmed death 1 receptor

213 CHB vs 61 controls examined.

- Greater sPD-1 levels in CHB compared to HC
- significant positive correlations with: ALT, AST, Tbili, HBV DNA, APRI, Fib4 (negative correl for platelets)
- Increased sPD-1 level with greater histological inflammation and fibrosis



Zhou et al, JVH 2019

Immunological serum biomarkers : clinical relevance

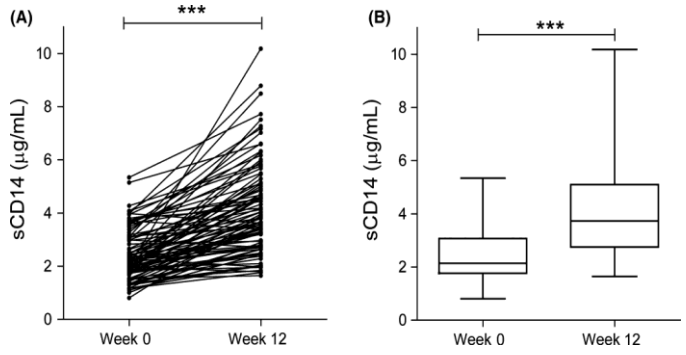
Outcome of antiviral therapy

- IP-10/CXCL10
- CXCL9/10/11/13, IL21
- sCD14

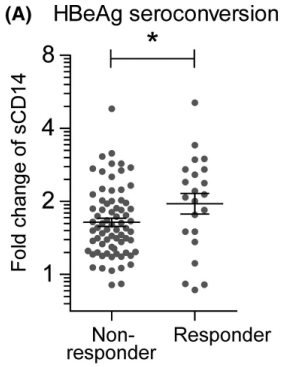
sCD14

sCD14: A marker of monocyte activation--increased with PEG IFN Tx and associated with HBeAg loss (? Also associated with cirrhosis progression?)

Increased sCD14 on PEG IFN therapy



Fold change in sCD14 +/- HBeAg loss at 26w post-Tx



Dou et al, JVH 2019

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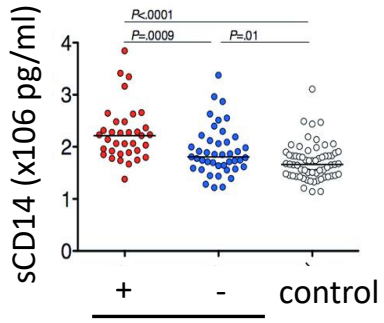

HBV or HCV with Cirrhosis progression

Sandler et al, Gastro 2012

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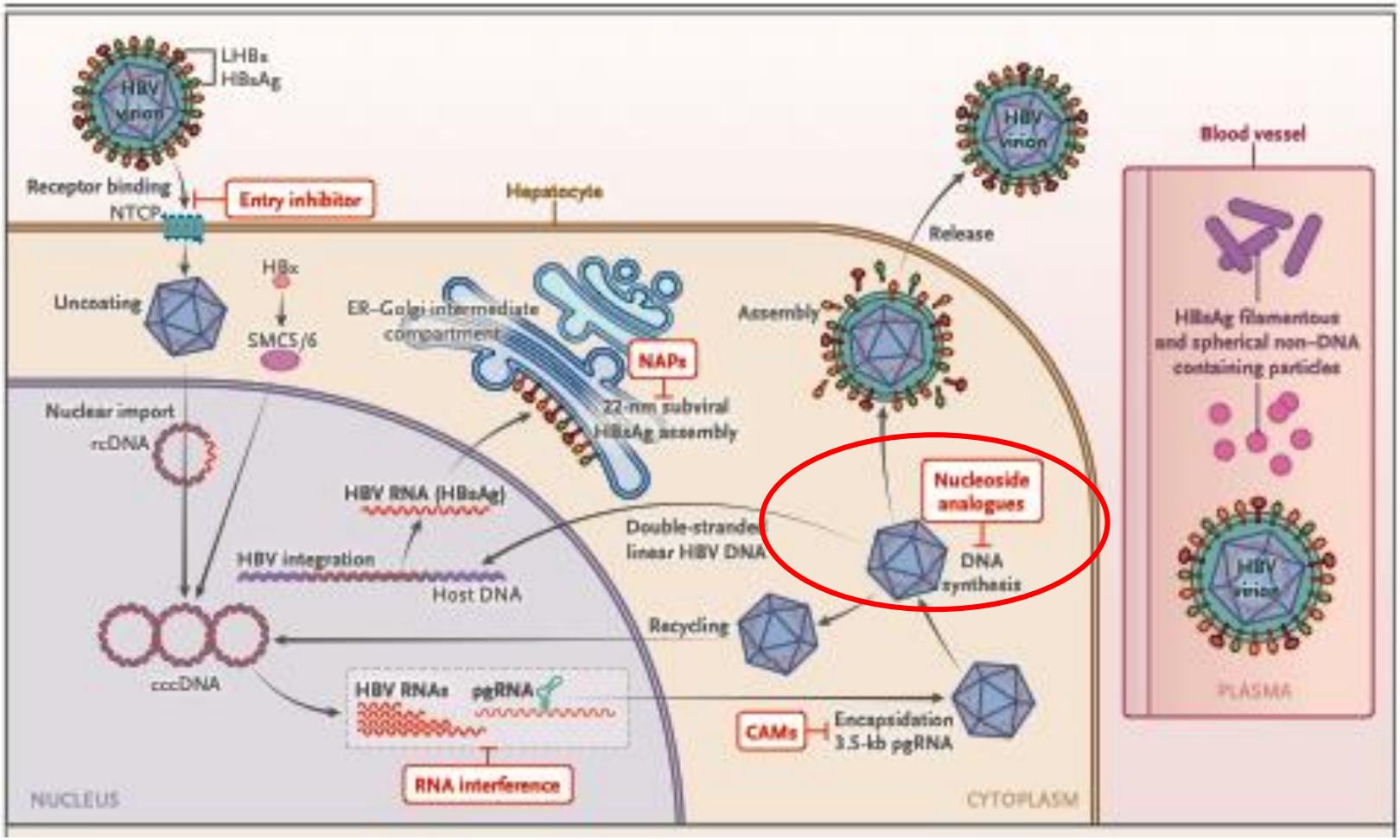
Disadvantages and Limitations of Nucleoside Analogues

Target a late stage in the viral life cycle

Kramvis A, Nat Rev Gastroenterol Hepatol. 2022
Mak LY, et al: Gut and Liver, 2019



Dusheiko G. N Engl J Med. 2023

Disadvantages and Limitations of Nucleoside Analogues

Target a late stage in the viral life cycle

→ not directly affect HBsAg expression from integrated genomes

Kramvis A, Nat Rev Gastroenterol Hepatol. 2022
Mak LY, et al: Gut and Liver, 2019

Compounds in Development for Chronic Hepatitis B

Treatment & Management
Medication Assistance Programs in the U.S.
Adults Living with Hep B
Children Living with Hep B
Pregnancy and Hep B
Treatment Options
Clinical Trials
Clinical Trial Survey
Physician Directory
Drug Watch

Drug Watch

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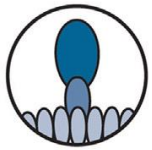
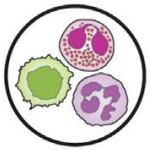
Compounds in Development for Chronic Hepatitis B

Updated May 12, 2023

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
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
Xalnesiran (RG6346, DCR HBVS)	RNAi gene silencer	Dicerna, USA with Roche	dicerna.com	Phase II
Imdurisan (AB-729)	RNAi gene silencer	Arbutus Biopharma, USA	arbutusbio.com	Phase II
ALG-125755	RNAi gene silencer	Aligos Therapeutics, USA	aligos.com	Holding for new partner
Entry Inhibitors: Interferes with HBV getting into liver cells				
Bulevirtide (Hepcludex)	Entry inhibitor	Gilead, USA	gilead.com	Phase III
Capsid or Core Inhibitors: Interferes with the viral DNA protein shield				
ZM-H1505R	Capsid inhibitor	Zhimeng Biopharma, PR China	core-biopharma.com	Phase II
EDP-514	Capsid inhibitor	Enanta Pharma, USA		
ALG-000184	Capsid inhibitor	Aligos Therapeutics, USA		
ABI-H4334	Capsid inhibitor	Assembly Biosciences, USA		
HBsAg Inhibitors: Interferes with production of HBV surfac				
REP 2139	sAg inhibitor	Replicor, Canada		
Antisense Molecules: Binds to the viral mRNA to prevent it				
Bepirovirsen	HBV Antisense	GSK, USA		
AHB-137	HBV Antisense	AusperBio, China		
Gene Editing: Intended to destroy or repress HBV DNA				
EBT107	CRISPR/Cas 9	Excision Bio, USA	excisi	
PBGENE-HBV	ARCUS platform	Precision Bio, USA	precis	
Immunologicals: Targets the human immune system to att				
Therapeutic Vaccine Technology used to stimulate the imn				
HeberNasvac	Therapeutic vaccine	CIGB, Cuba		
HepTcell	Therapeutic vaccine	Altimmune, USA		
VBI-2601 (BRII-179)	Therapeutic vaccine	VBI Vaccines, USA		
VVX001	Therapeutic vaccine	Viravaxx, Austria		
GSK 3528869A	Therapeutic vaccine	GSK, USA		
VTP-300	Therapeutic vaccine	Vaccitech, UK		
CVI-HBV-002	Therapeutic vaccine	Cha Vaccine Institute, S. Korea		
HB-400 (GS2829/GS6779)	Therapeutic vaccine	HOOKIPA Pharma, I Austria, with Gilead		
ISA104	Therapeutic vaccine	ISA Pharma, The Netherlands		
CARG-201	Therapeutic vaccine	CaroGen, USA		
TherVacB	Therapeutic vaccine	Helmholtz Zentrum Muenchen, Germany		
PRGN-2013	Therapeutic vaccine	Precigen		
VRON-0200	Therapeutic vaccine	Virion Therapeutics, USA		
Compounds that activate the innate immune system				
Selgantolimod (GS9688)	TLR-8 agonist	Gilead Sciences, USA	gilead.com	Phase II
Ruzotolimod (RG7854)	TLR-7 agonist	Roche, Switzerland	roche.com	Phase II
CB06	TLR-8 agonist	Zhimeng Biopharma, PR China	core-biopharma.com	Phase I
GSK 5251738	TLR-8 agonist	Gilead, USA	gilead.com	Phase I
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				
VIR-3434	Monoclonal antibody	Vir Biotech, USA	vir.bio	Phase II
Burfiralimab (IgG4)	Monoclonal antibody	ImmuneMed, South Korea	immunemed.co.kr/eng	Phase II
BJT-778	Monoclonal antibody	Blue Jay Therapeutics, USA	bluejaytx.com	Phase I
RG6449	Monoclonal antibody	Roche	roche.com	Phase I
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
RG6084	PDL1 inhibitor	Roche	roche.com	Phase II
AB-101	PDL1 inhibitor	Arbutus	arbutusbio.com	FDA hold 4/25/23
Other Immunologicals				
IMC-I109V	T-cell Receptor	Immunocore	immunocore.com	Phase I
Additional HBV Drugs Under Investigation				
GSK 4388067A	Targeted immunotherapy	GSK, USA	gsk.com	Phase II
EYP001	FXR agonist	Enyo Pharma, France	enyopharma.com	Holding for new partner
APG-1387	Apoptosis inducer	Ascentage, PR China	ascentagepharma.com	Phase II
GSK 3965193	PAPD5/PAPD7 inhibitor	GSK, USA	gsk.com	Phase I
DF-006	Small molecule	Drug Farm, Shanghai	drug-farm.com	Phase I
AB359	CD8 IL-2 immunotherapy	Asher Biotherapeutics, USA	asherbio.com	Preclinical
BJT-628	Small molecule	Blue Jay Therapeutics, USA	bluejaytx.com	Preclinical

New anti-HBV strategies

Replication inhibition	±	Antigen reduction	±	Immune modulation
Entry inhibitors: Bulevirtide **HBV polymerase:** HS-10234 **Capsid inhibitors:** GLS4 Canocapavir EDP-514 ABI-H3733 ALG-000184 ABI-4334		**HBsAg release:** REP 2139 **ASOs:** Bepirovirsen **siRNAs:** JNJ-3989 VIR-2218 RG6346 AB-729 ALG-125755		**Immune invigoration:** Selgantolimod RG7854 Envafolimab **Immune stimulation:** HepTcell TG-1050/T101 GSK3528869A VTP300 **Monoclonal Abs against HBV:** VIR-3434

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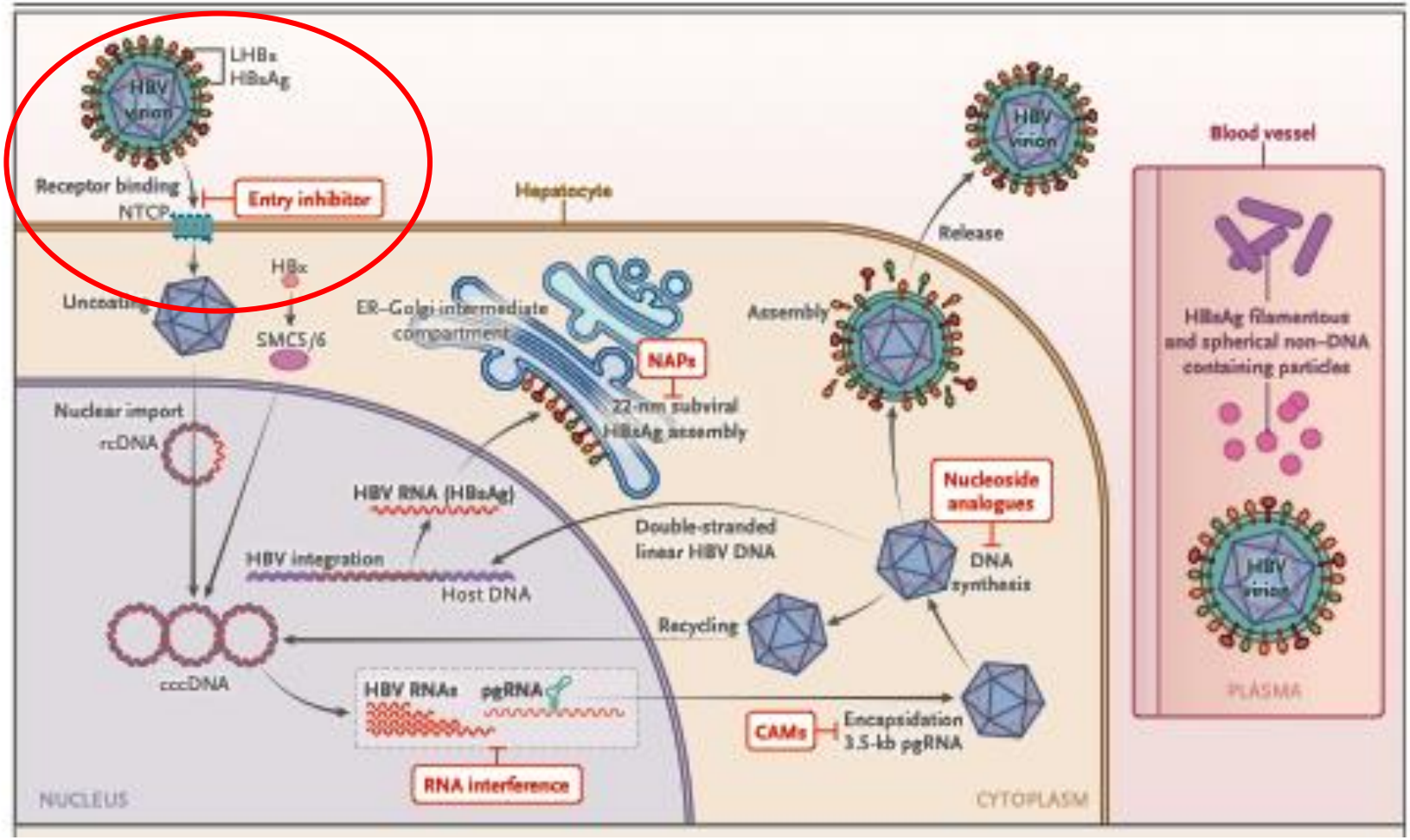
New anti-HBV strategies



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Entry Inhibitors

Bulevirtide

→ a synthetic pre- S1 lipopeptide, binds to and inactivates the sodium taurocholate cotransporting polypeptide, inhibiting entry of HBV (and hepatitis D virus)

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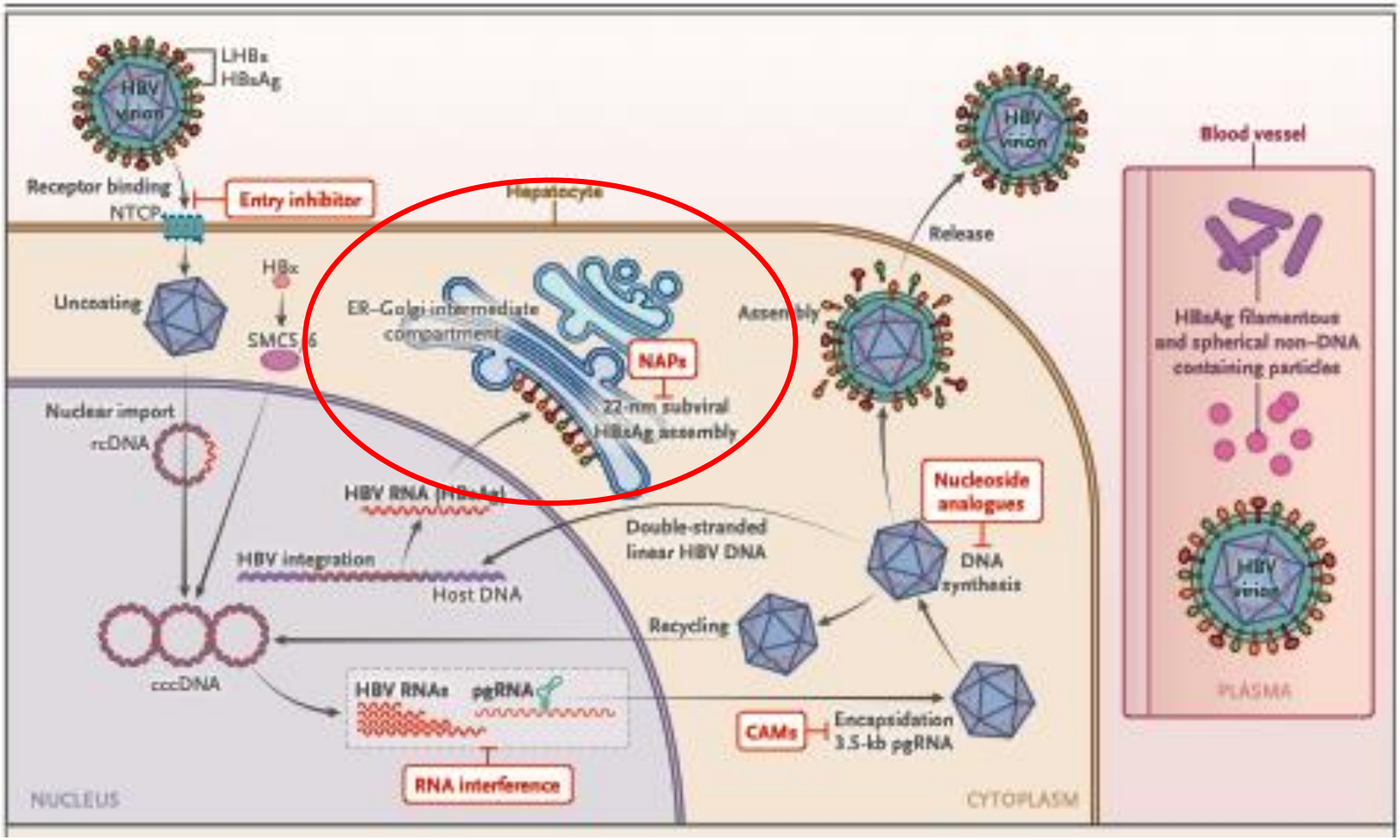
New anti-HBV strategies



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Nucleic acid polymers

NAPs are oligonucleotides → act as HBsAg release inhibitors

REP 2139 tested in combination with TDF and p-INF

→ After 48w FU HBsAg was undetectable in 14 of 40 study participants.

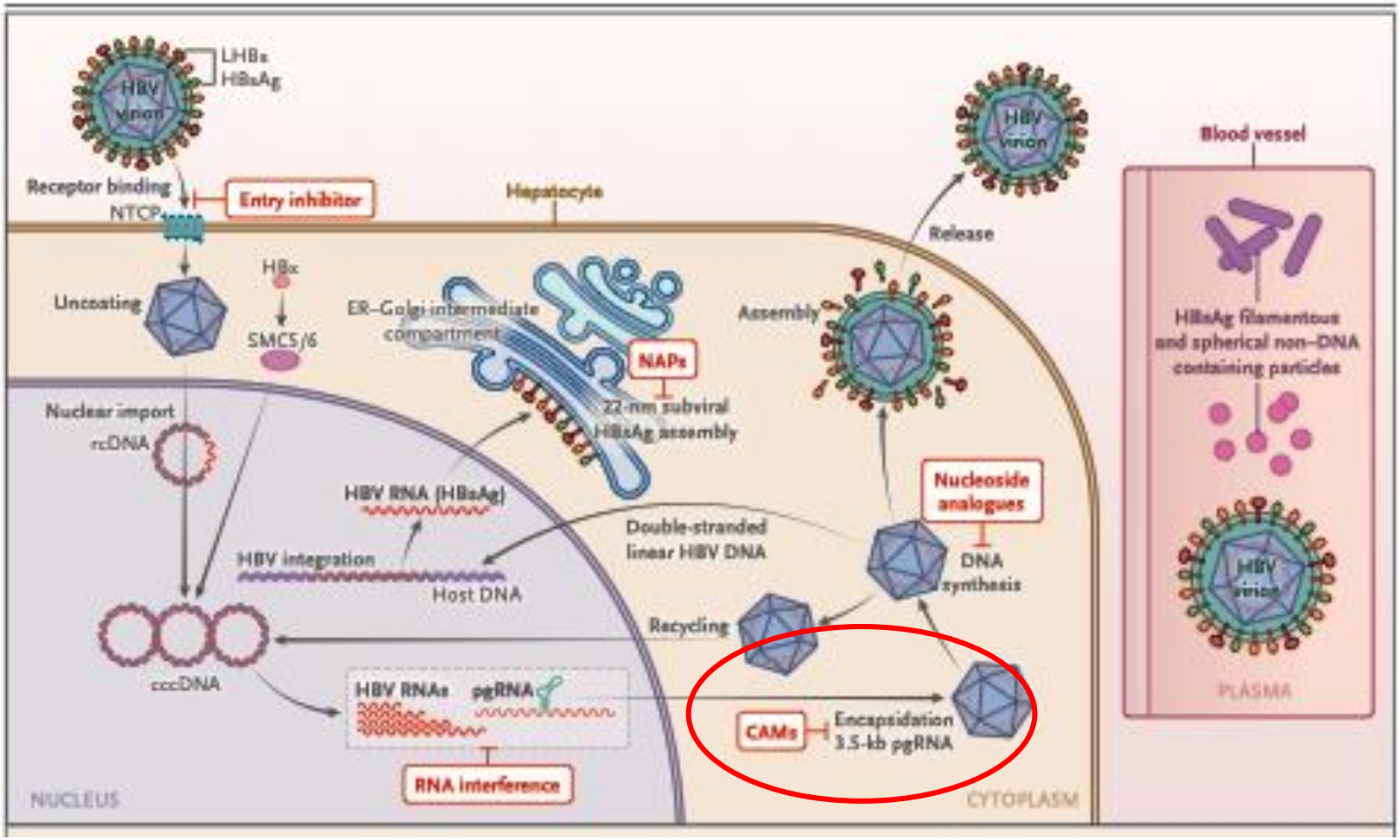
→ ALT flares during treatment are indicative of immune reconstitution

Jules Levin
AASLD Nov 2019

Table 3. REP 401 Treatment and Follow-up Summary

Patients entered into trial		**40**
End of treatment HBsAg response	> 1 log from baseline	36 (90%)
	< 1 IU/mL	27 (67%)
	≤ 0.05 IU/mL	24 (60%)
Patients currently completed treatment and 24-48 weeks of follow-up		**34**
Stable, inactive HBV (HBV DNA ≤ 2000 IU/mL, normal ALT)		15 (44%)
Functional cure (HBsAg and HBV DNA target not detected)		14 (41%)
Therapy not indicated (AASLD / EASL guidelines) Clinical benefit (Low risk of fibrosis progression and HCC)		29 (85%)

New anti-HBV strategies



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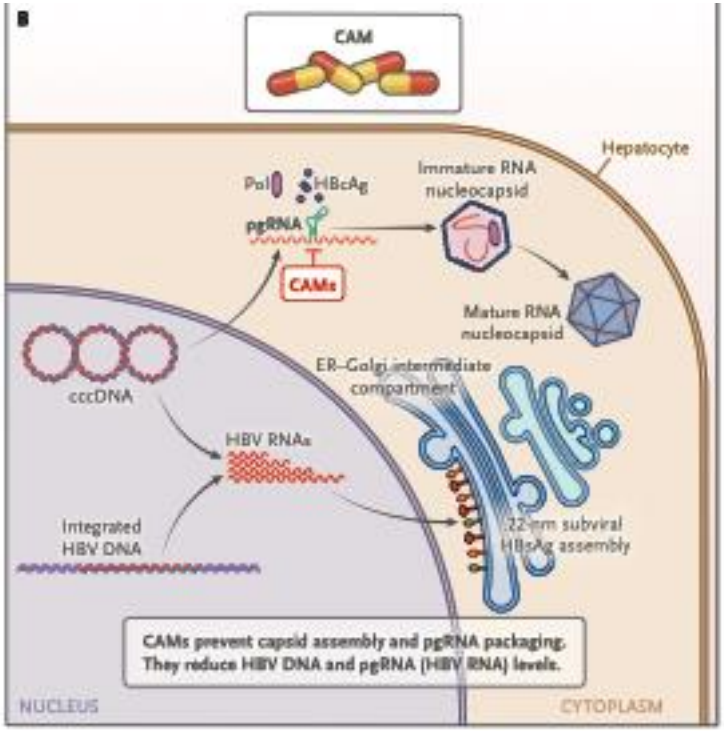
Capsid Assembly Modulators

Decreases in serum HBV DNA levels and HBV RNA levels within 28 days

Do NOT reduce established cccDNA levels or transcription from cccDNA

→ have no direct effect on HBsAg.



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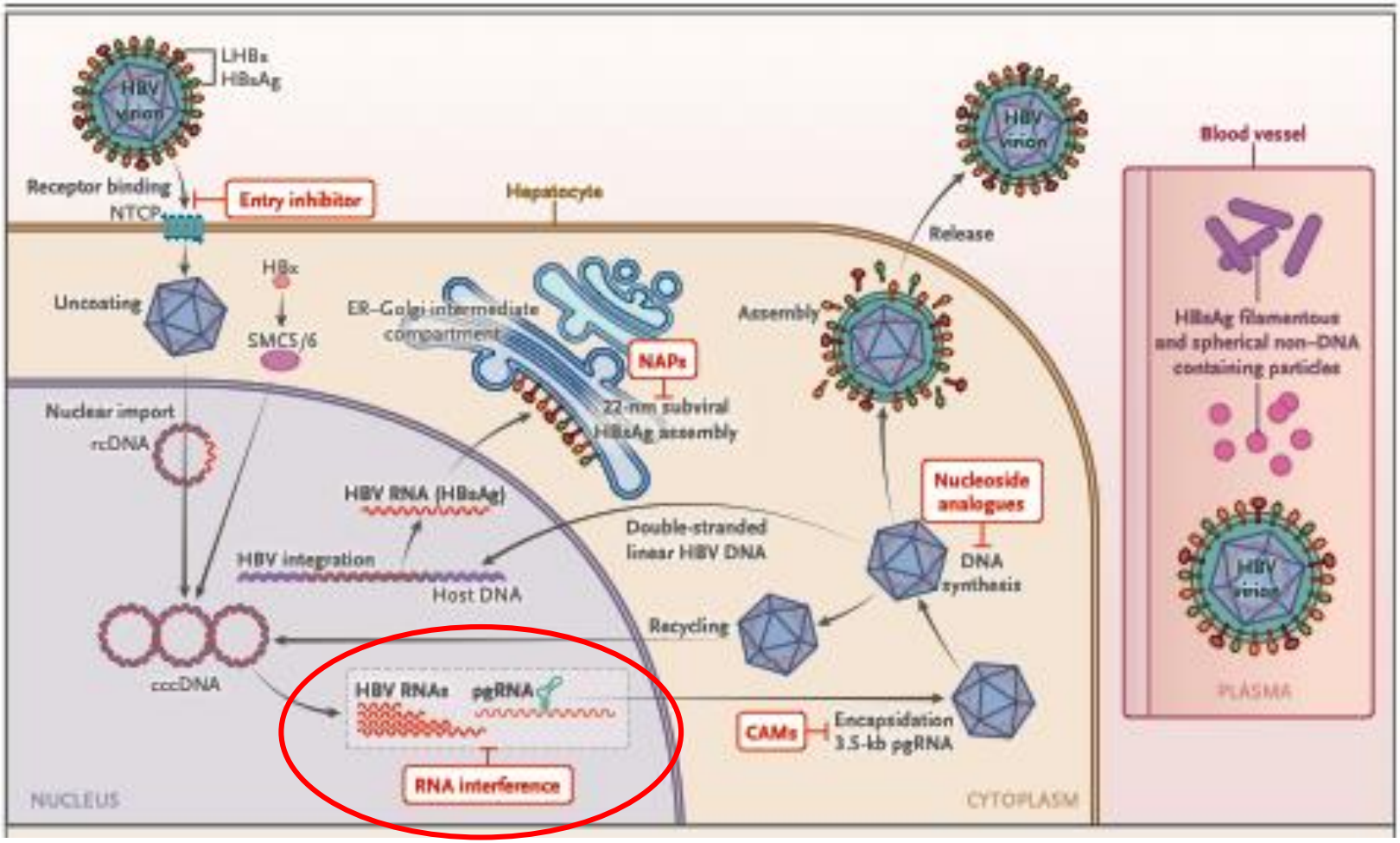
New anti-HBV strategies



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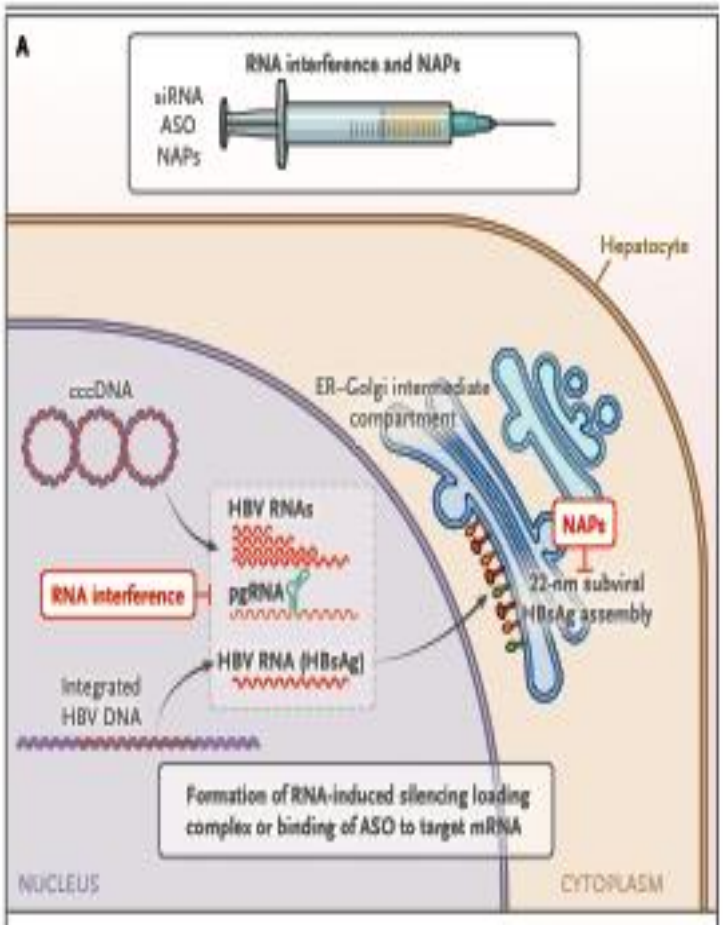
small interfering RNA

siRNA interfere with viral mRNA to prevent synthesis of viral antigens



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REEF-2 Study

- JNJ-3989 is an siRNA that targets all HBV RNAs, thereby reducing levels of all viral proteins[1]
- JNJ-6379 is a CAM-N that inhibits viral replication by inducing the formation of structurally normal, non-infectious viral particles consisting of empty nucleocapsids[2]
- In the REEF-1 study (NCT03982186), JNJ-3989, with or without JNJ-6379, demonstrated strong dose-dependent HBsAg decline in a 48-week regimen[3]
- In virologically suppressed, NA-treated, non-cirrhotic, HBeAg negative CHB patients, discontinuation of NA treatment may result in increased rates of functional cure (HBsAg seroclearance), especially in the subset of patients with low HBsAg levels at the end of treatment[4]
- The REEF-2 study (NCT04129554) assessed the efficacy and safety of 48 weeks of the combination of JNJ-3989, JNJ-6379, and NA in this population, with 48 weeks of follow-up after discontinuation of all treatment
  - Here, we report Follow-up Week 24 data

CAM-N, capsid assembly modulator - normal capsid structure; CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, nucleos(t)ide analogues; siRNA, small interfering RNA.

1. Yuen MF, et al. Submitted. 2022. 2. Berke JM, et al. *Antimicrob Agents Chemother*. 2020; 64(5):e02439-19. 3. Yuen MF, et al. AASLD: The Liver Meeting; Nov, 2021; abstract LO10. 4. Van Bommel F and Berg, T. *Hepatology Commun*. 2021;0:1-17.

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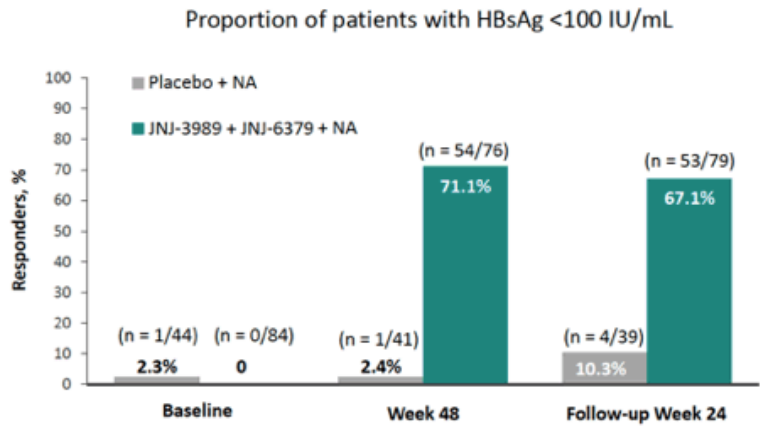
REEF-2 Study

REEF-2: Primary Endpoint and Proportion of Patients With HBsAg <100 IU/mL

No patients achieved the primary endpoint of HBsAg seroclearance* at Follow-up Week 24 without restarting NA treatment, in either treatment arm



*HBsAg seroclearance defined as HBsAg <LLOQ (0.05 IU/mL).

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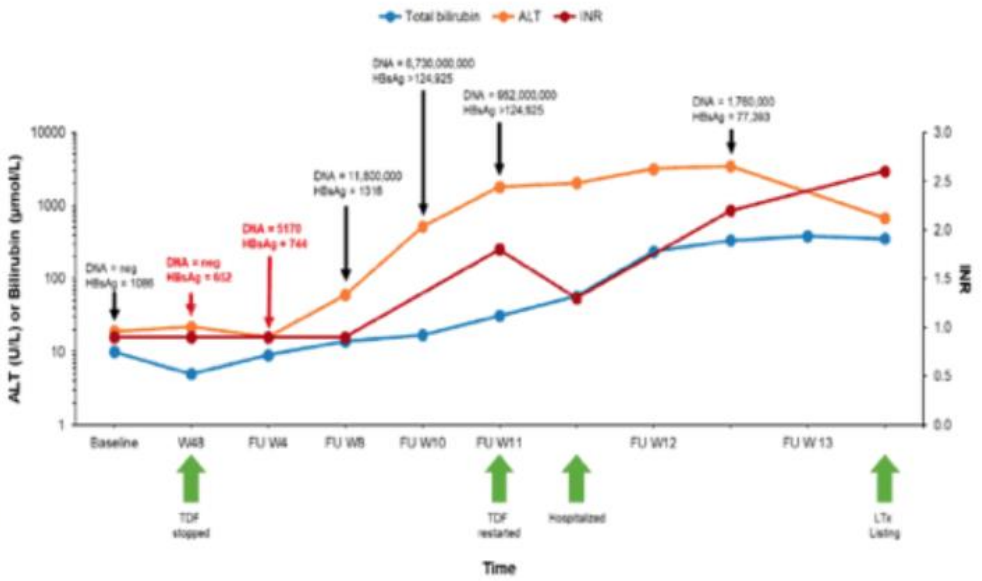
REEF-2 Study

REEF-2: Subacute Liver Failure Following NA Withdrawal

- 54-year-old, Asian male with stable TDF treatment for 8 years prior to screening
- NA only treatment arm
- Follow-up Week 11: rise in HBV DNA and ALT after stopping NA prompted NA retreatment, with jaundice, coagulopathy, and sub-acute liver failure
- Super-urgent listing and liver transplant required, with complete recovery
- Prompted an amendment to retreatment criteria: HBV DNA >5 $\log_{10}$ IU/mL requires immediate retreatment irrespective of ALT increase



HBV DNA and HBsAg values shown as IU/mL.

Agarwal et al. *J Hepatol.* 2022;77(1):245-248. doi: 10.1016/j.jhep.2022.03.006.

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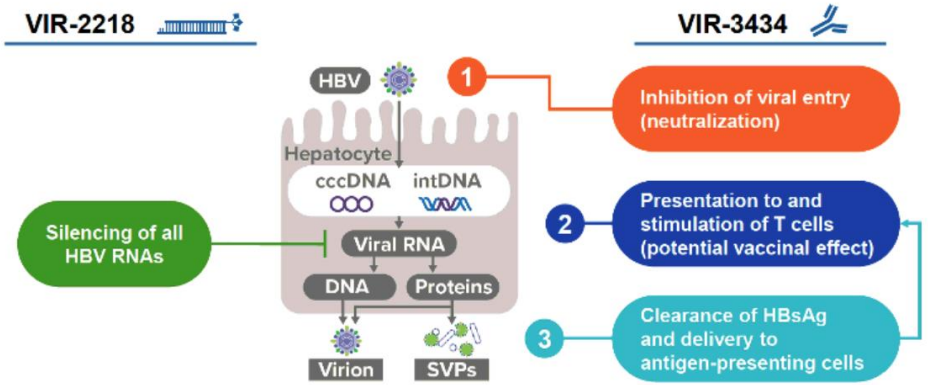
MARCH Study

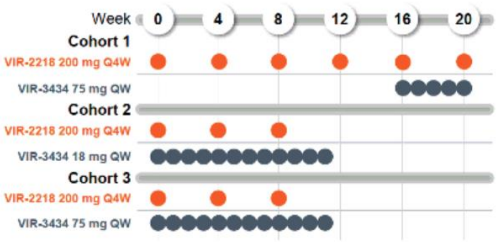
VIR-2218 and VIR-3434 Target Different Steps in the HBV Replication Cycle[1]



1. Lempp FA, Volz T, Cameroni E, et al. 2022. doi: 10.1101/2022.09.09.507326
Abbreviations: cccDNA, covalently closed circular DNA; DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; intDNA, integrated DNA; RNA, ribonucleic acid; SVPs, subviral particles.

EASL 2023 OS-031

MARCH Part A: Preliminary Low-Dose, Short-Duration Regimens of VIR-2218 Plus VIR-3434



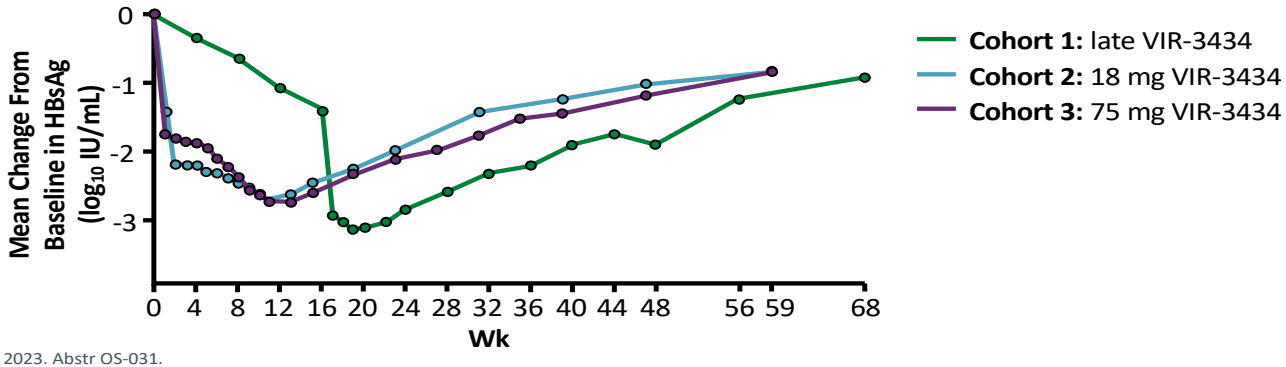
- Part A cohorts were designed to rapidly assess the safety and potential additive antiviral activity of VIR-2218 plus VIR-3434
- Lead-in and simultaneous treatment approaches were evaluated to assess the contribution of each component
- Enrollment in cohort 2 was limited due to emerging phase 1 data enabling evaluation of higher VIR-3434 dose levels

Abbreviations: QW, once weekly; Q4W, once every 4 weeks.

EASL 2023 OS-031

MARCH: Efficacy of VIR-2218 + VIR-3434 for Virologically Suppressed CHB

- 90% achieved HBsAg <10 IU/mL by EoT
- **No participants achieved HBsAg loss**
- HBsAg **gradually rebounded** after EoT in all cohorts
  - **Remained almost 1 log_{10} IU/mL below baseline** for 48 wk after EoT
- 6 patients discontinued NA therapy; **4/6 remained off NA** as of last available follow-up



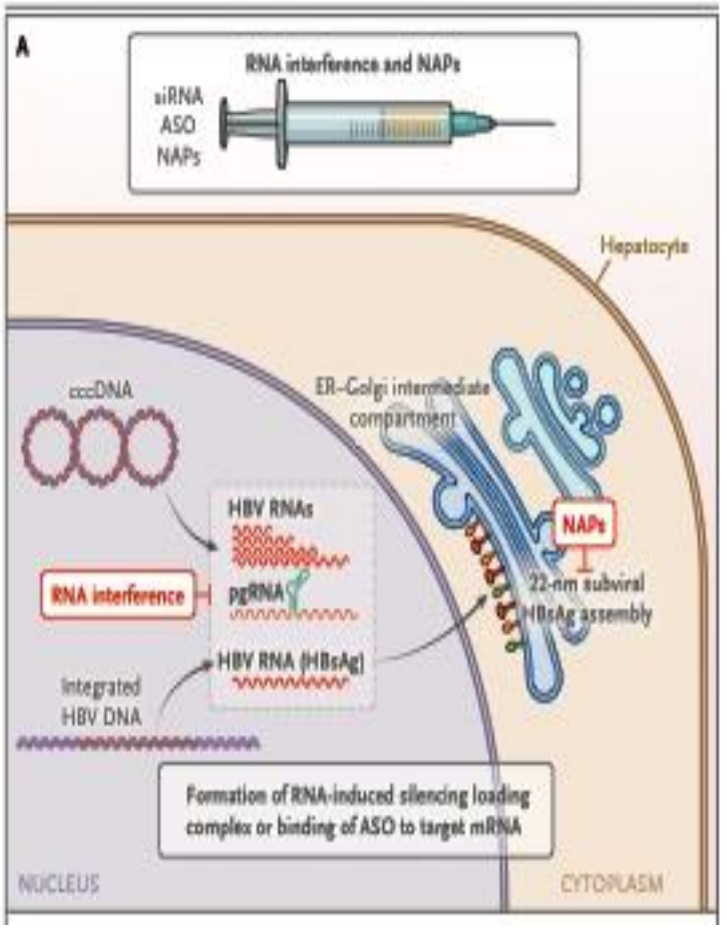
Gane. EASL 2023. Abstr OS-031.

Antisense oligonucleotides

Bepirovirsen

targets all HBV RNA and impacts HBV infection in three distinct ways:

- reductions in viral proteins (HBsAg)
- reductions in HBV DNA
- stimulation of the immune system



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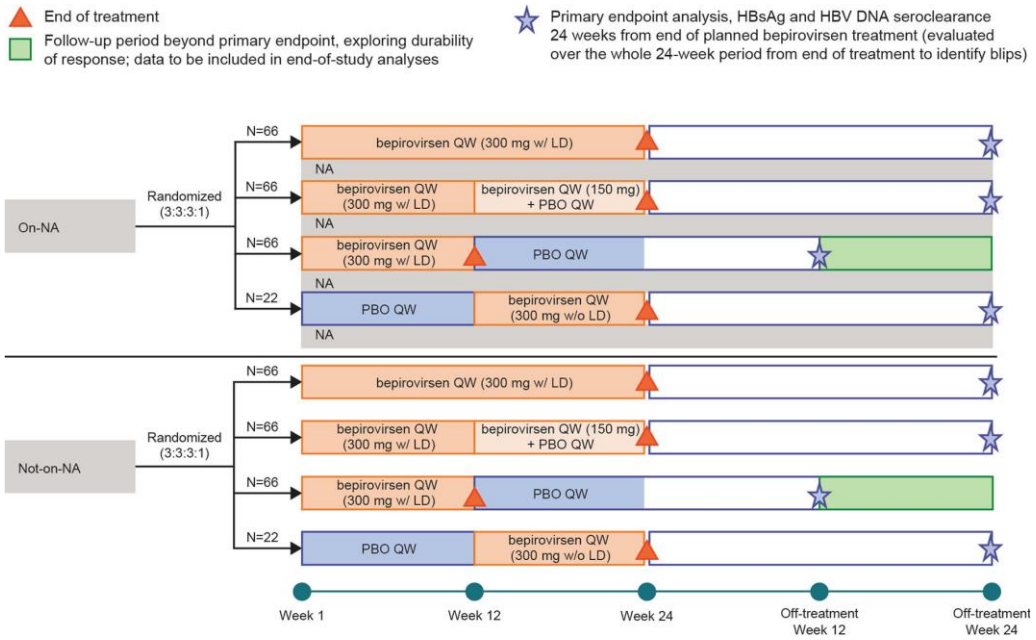
Bepirovirsen

In the Phase 2b, randomised, B-Clear study

→ 32 participants On-NA and Not-on-NA achieved HBsAg <0.05 IU/mL and HBV DNA level <20 |U/mL



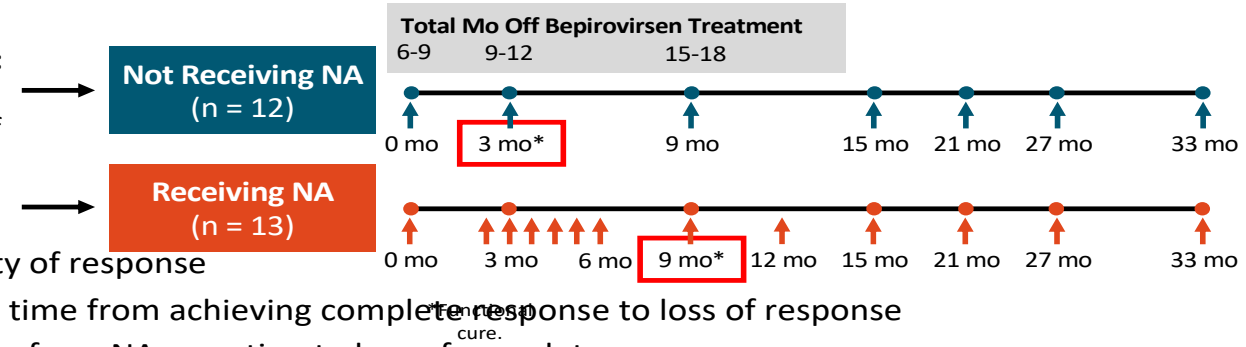
Yuean. N Engl J Med 2022;

Bepirovirsen

B-Sure First Annual Report: Long-term Follow-up of Complete Responders to Bepirovirsen in B-Clear Trial

- Phase II analysis of people with CHB who responded to bepirovirsen with and without NA
- **Assess durability of response** and **provide option for cessation** for patients receiving NA

B-Clear complete responders:
HBsAg <0.05 IU/mL and HBV DNA <20 IU/mL at end of bepirovirsen treatment
(N = 25)



*End of treatment cure.

- **Endpoints**: durability of response
  - **Not receiving NA:** time from achieving complete response to loss of response
  - **Receiving NA**: time from NA cessation to loss of complete response

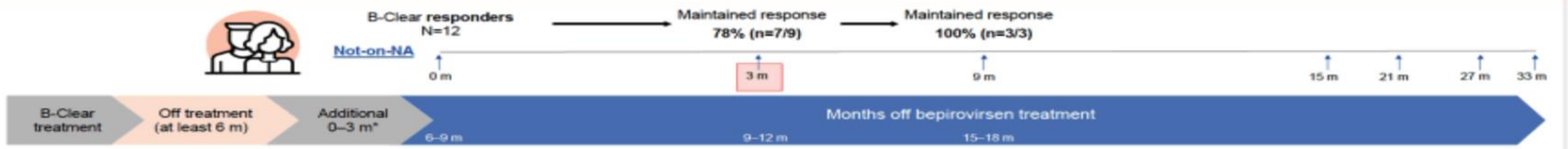
Gadano. EASL 2023. Abstr LBP-15.

Bepirovirsen

Not-on-NA population:

- Of the 9 participants with ≥3 months of follow-up within B-Sure, 78% (7/9) maintained response (**Figure 2**). No participant met NA restart criteria.
- Of the 3 participants with ≥9 months of follow-up within B-Sure, 100% (3/3) maintained response (≥15–18 months after end of bepirovirsen).

Figure 2. Responders from the Not-on-NA population maintained durable treatment response off all treatment

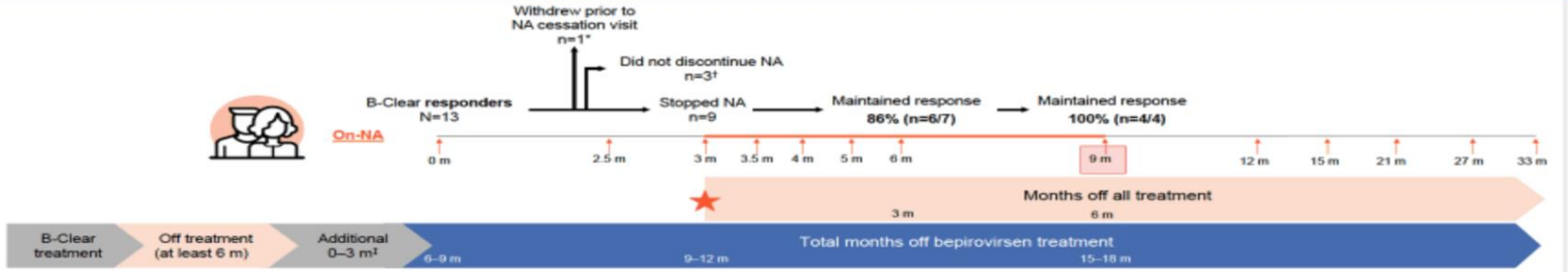


*Mean duration between B-Clear end-of-study and entry into B-Sure: 84 days (range 0–105). Red box: equivalent to functional cure, all Not-on-NA patients have at least 36 weeks off all treatment (allowing for bepirovirsen wash out).

On-NA population:

- 69% (9/13) participants ceased NA as per protocol.
- Of the 7 participants who ceased NA and had ≥6 months of follow-up within B-Sure, 86% (6/7) maintained response 3 months post NA cessation (**Figure 3**).
- Of the 4 participants who ceased NA and had ≥9 months of follow-up within B-Sure, 100% (4/4) maintained response 6 months post NA cessation; no participants restarted NAs.

Figure 3. Responders from the On-NA population maintained durable treatment response off all treatment



*8% (1/13) withdrew prior to NA cessation due to commitments; †23% (3/13) were not eligible to cease NA (2 did not meet protocol defined criteria for cessation due to detectable HBsAg and 1 due to investigator discretion despite HBsAg <0.05 IU/mL) – Eligibility to discontinue NA: HBsAg <0.05 IU/mL and HBV DNA <LLOQ and ALT <1.25 ULN and on stable NA, investigator discretion, evidence of prior or current cirrhosis, or participant preference; ‡Mean duration between B-Clear end-of-study and entry into B-Sure: 102 days (range 94–113). Red box: equivalent to functional cure, all On-NA participants have at least 24 weeks off NA therapy.
ALT, alanine aminotransferase; ULN, upper limit of normal.

*8% (1/13) withdrew prior to NA cessation due to commitments; †23% (3/13) were not eligible to cease NA (2 did not meet protocol defined criteria for cessation due to detectable HBsAg and 1 due to investigator discretion despite HBsAg <0.05 IU/mL) – Eligibility to discontinue NA: HBsAg <0.05 IU/mL and HBV DNA <LLOQ and ALT <1.25 ULN and on stable NA, investigator discretion, evidence of prior or current cirrhosis, or participant preference; ‡Mean duration between B-Clear end-of-study and entry into B-Sure: 102 days (range 94–113). Red box: equivalent to functional cure, all On-NA participants have at least 24 weeks off NA therapy.
ALT, alanine aminotransferase; ULN, upper limit of normal.

Gadano. EASL, 2023

Immunomodulatory Therapy

Therapeutic goal is to achieve sustained virus control with immune restoration by suppressing viral antigen expression and the viral life cycle

Strong rationale to examine how the immune phenotype and function are affected by novel therapies, including immune-modulatory therapies

Immunomodulatory Therapy

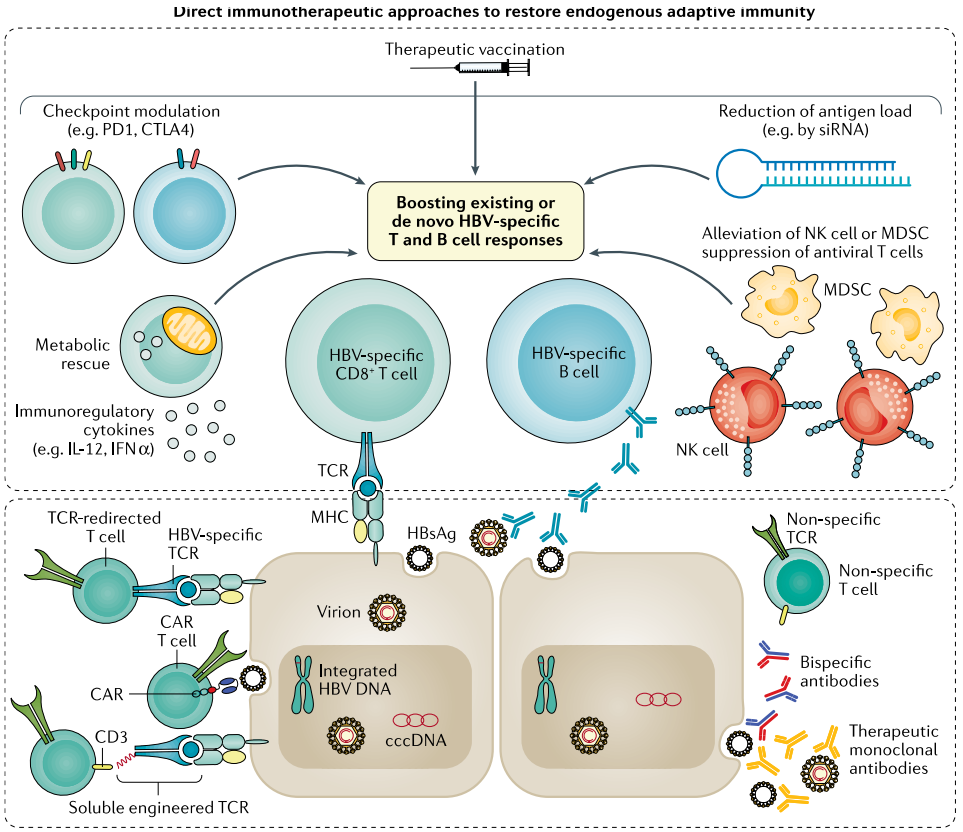
Box 2 | **Restoration or replacement immunotherapies**

Restoration

- Therapeutic vaccination*
- PD1 blockade*
- Alternative T cell and B cell checkpoint blockade
- TLR agonists*
- Metabolic or mitochondrial targets
- Blockade of regulatory interactions (for example, NK cells)
- Reduction of antigen load*

Replacement

- TCR-redirected T cells*
- CAR T cells
- Soluble TCRs (for example, ImmTAVs)
- Monoclonal antibodies*
- Bispecific antibodies



Immunomodulatory Therapy

Studies in humans of innate approaches have included **TLR7 and TLR8 agonists and RIG-I agonists** (along with IFN). Attempts to enhance HBV-specific T cell responses have focused **on therapeutic vaccines and interruption of the programmed death 1 (PD1)/pro- grammed death ligand 1 (PDL1) axis**

Immunomodulatory compounds			
Immune invigoration			
Selgantolimod (GS-9688)	TLR8 agonist	II	NCT03615066
		II	NCT03491553
RG7854	TLR7 agonist	II	NCT04225715
Envafolimab (ASC22)	PDL1 inhibitor	II	NCT04465890
Immune stimulation			
HepTcell (FP-02.2)	Therapeutic vaccine	II	NCT04684914
			NCT04465890
TG-1050/T101	Therapeutic vaccine	II	NCT04189276
GSK3528869A	Therapeutic vaccine	II	NCT05276297
		I/II	NCT03866187
VTP300	Therapeutic vaccine	II	NCT05343481
		I/II	NCT04778904

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Take home messages

Defining realist endpoints

HBcrAg and serum HBVRNA are promising surrogate markers of cccDNA activity

More translational studies coupling intrahepatica and serum biomarkers

Prevent HBV infection → vaccination

Prevention is better than cure

Thank you for your attention !!!