Terapia antivirale di HBV: quali prospettive per i nostri pazienti

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Università di Pavia.
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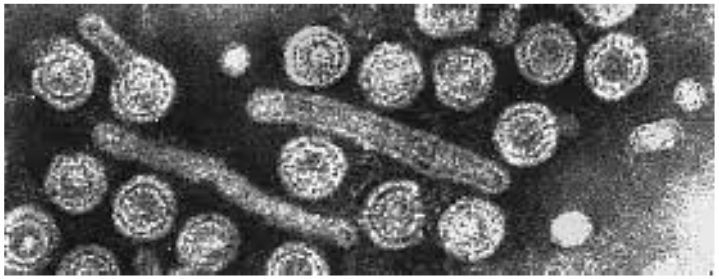
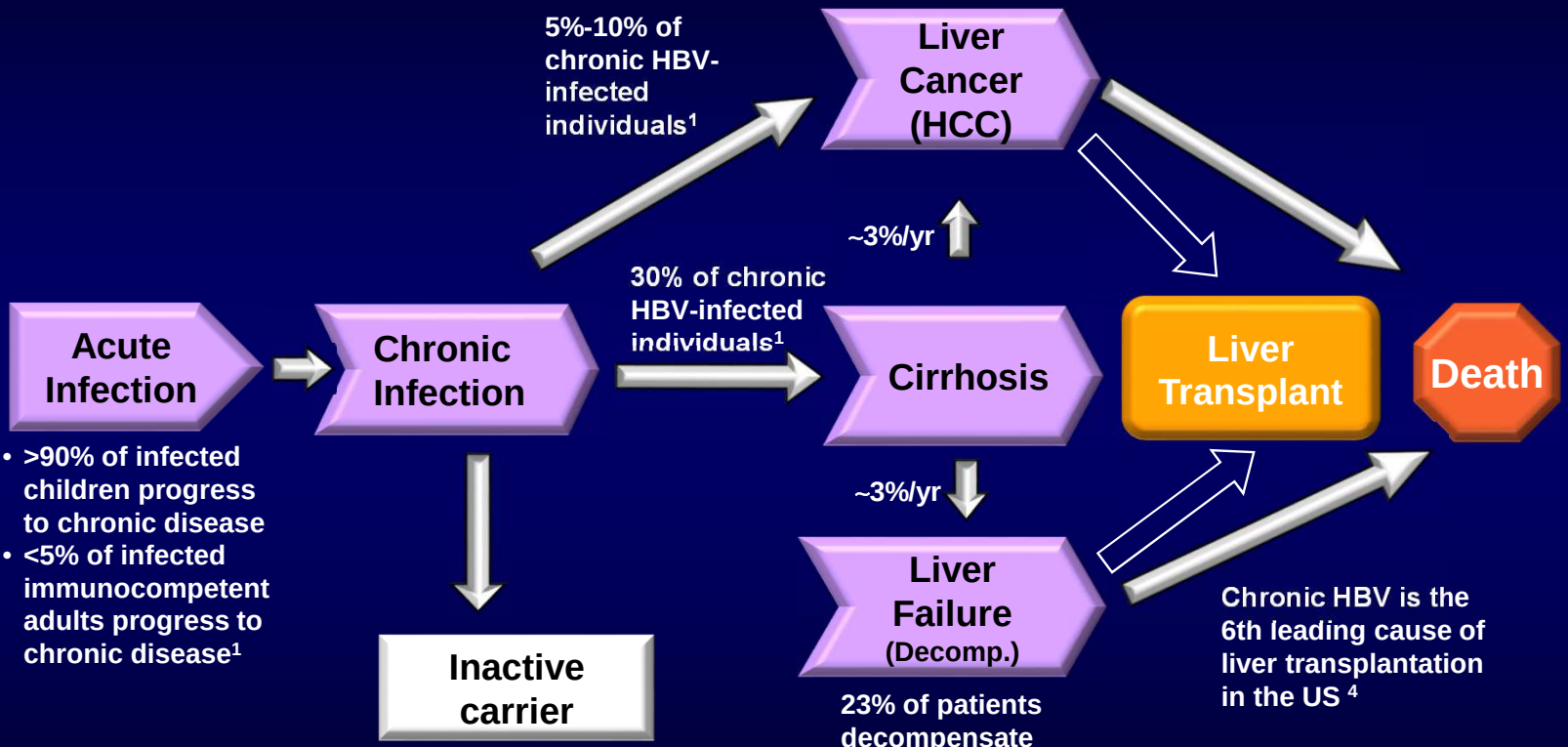
Fondazione IRCCS Policlinico San Matteo.

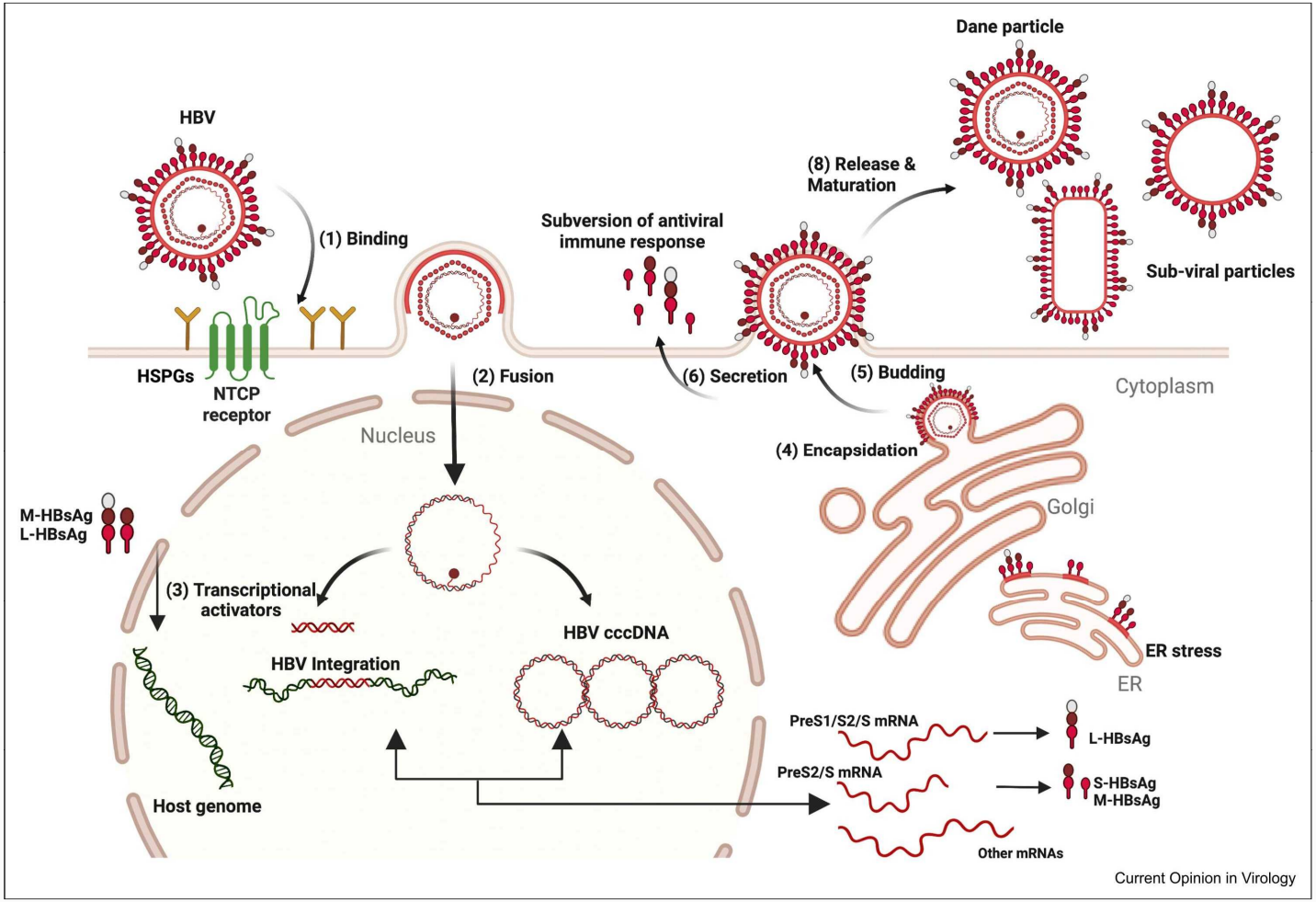


Natural History of Hepatitis B Virus Infection



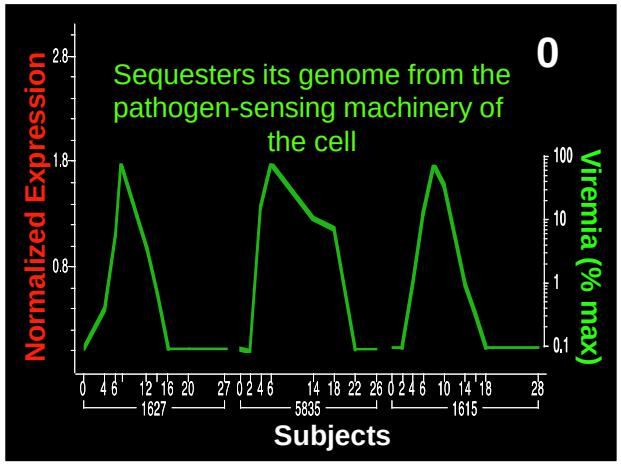
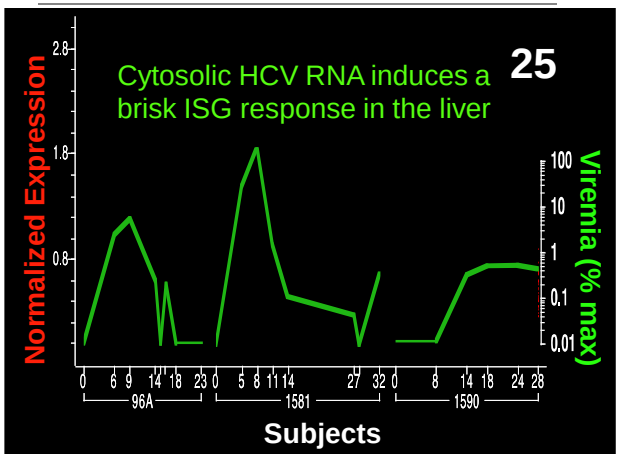
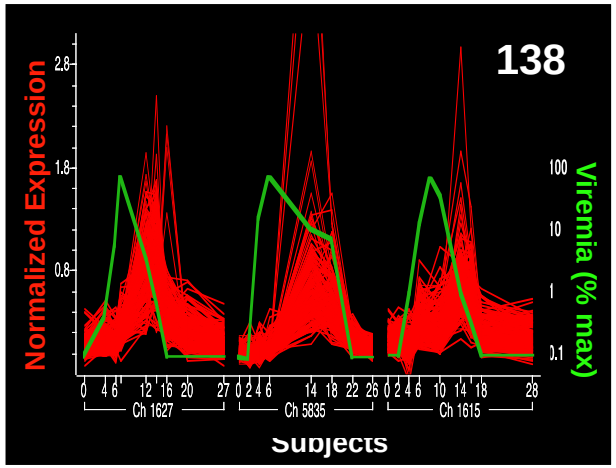
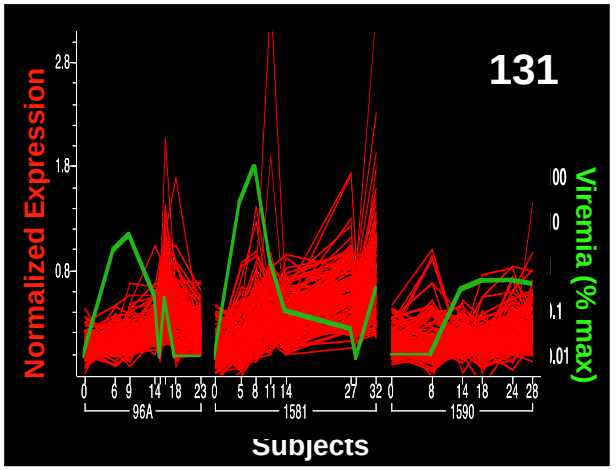
1. Torresi, J, Locarnini, S. Gastroenterology. 2000.
2. Fattovich, G, Giustina, G, Schalm, SW, et al. Hepatology. 1995.
3. Moyer, LA, Mast, EE. Am J Prev Med. 1994.
4. Perrillo, R, et al. Hepatology. 2001.

HBV Replication Cycle



Nasser N, et al. *Curr Opin Virol* 2023 Sep 9;101360.

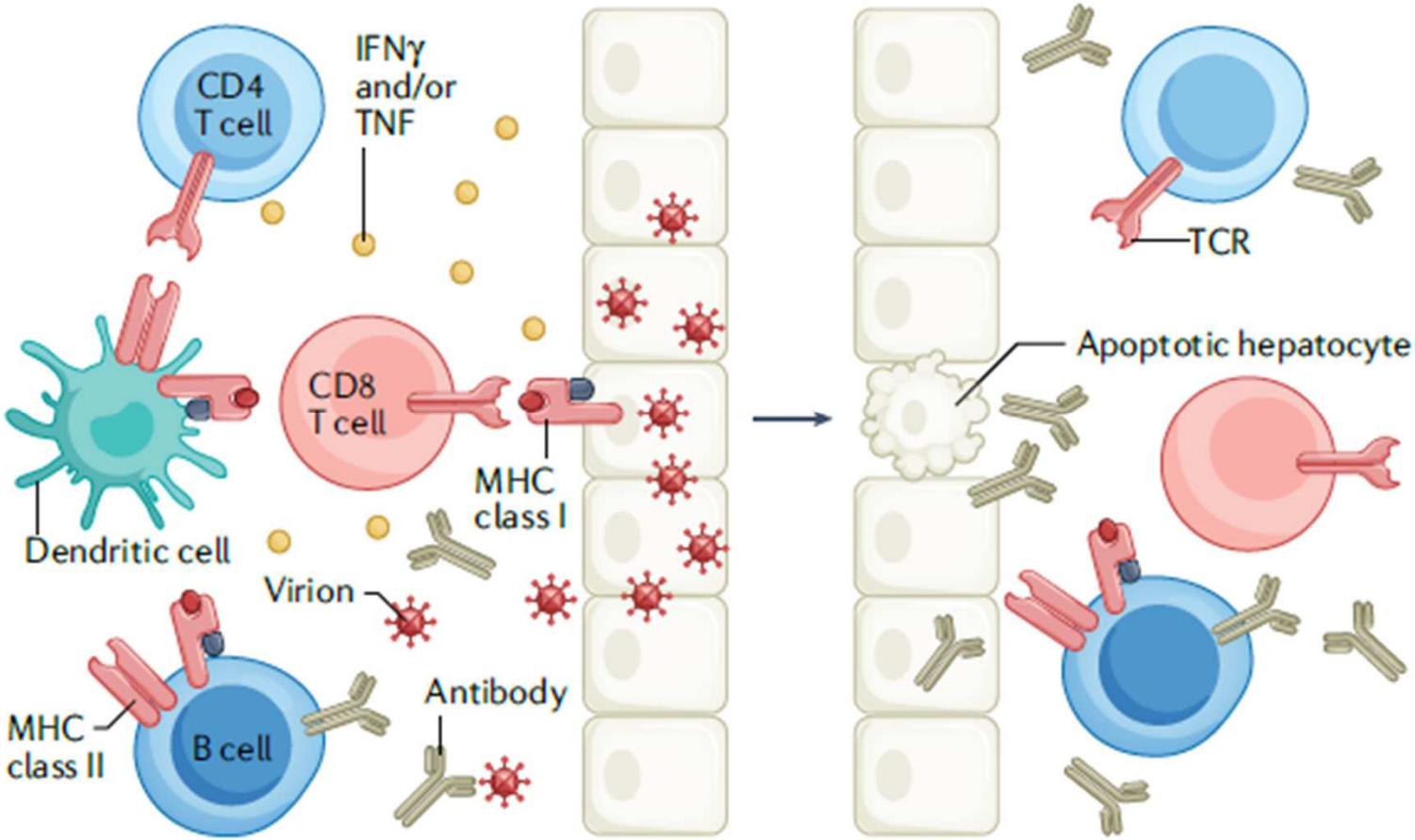
Does Acute HBV Infection Trigger an Innate Host Response in the Liver?

	HBV	HCV
Genes that track with viremia *Interferon-Stimulated genes*		
Genes that track with clearance *T cell genes & T cell-induced genes*		

Su et al *PNAS* 2002

Courtesy of Frank Chisari

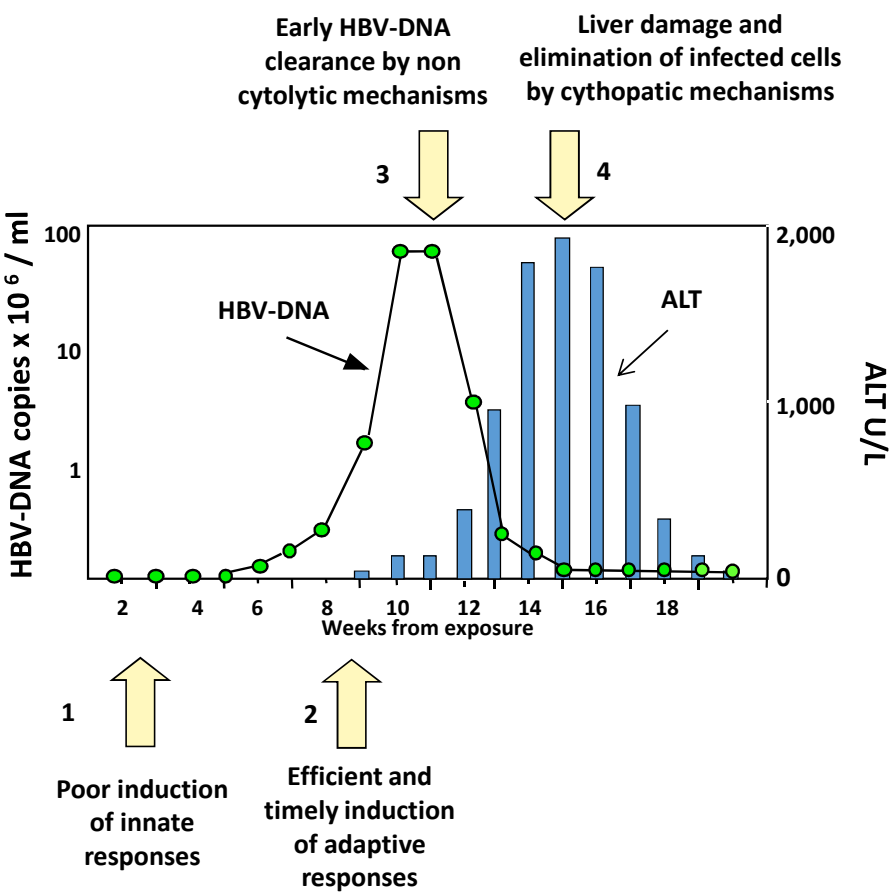
HBV-Specific Adaptive Immune Responses



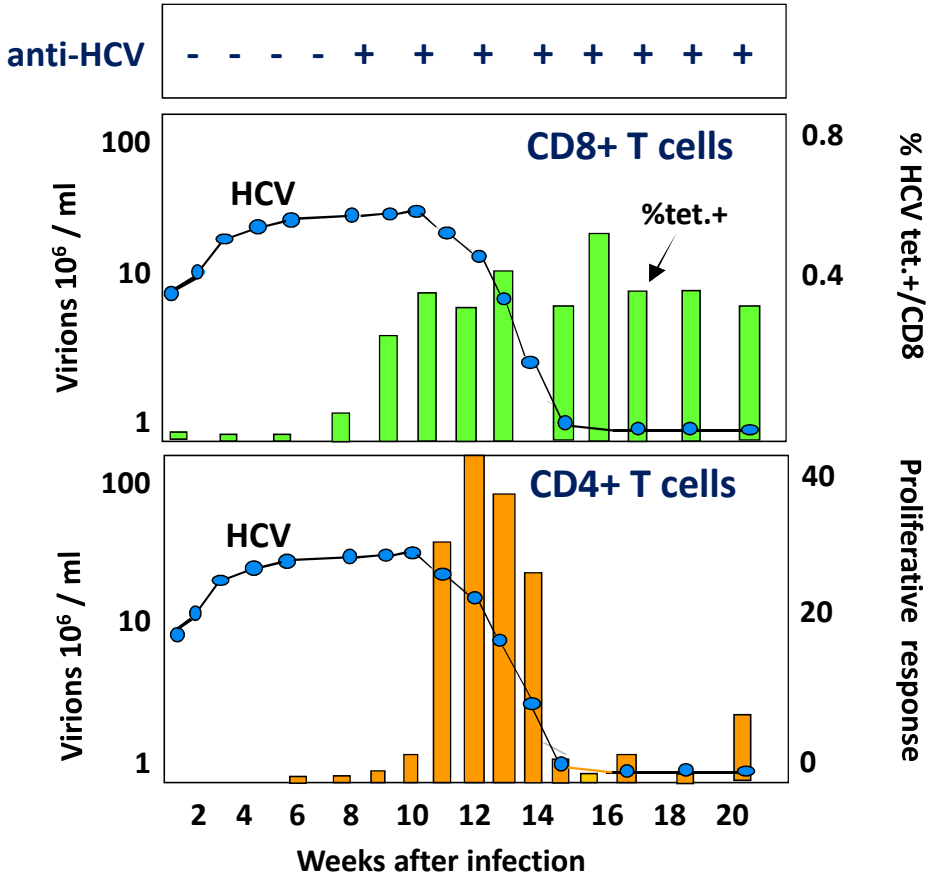
Kramvis A, et al. *Nat Rev Gastroenterol Hepatol*. 2022;19:727-74

Rapid Establishment of HCV Replication Outpaces Adaptive Immunity

HBV



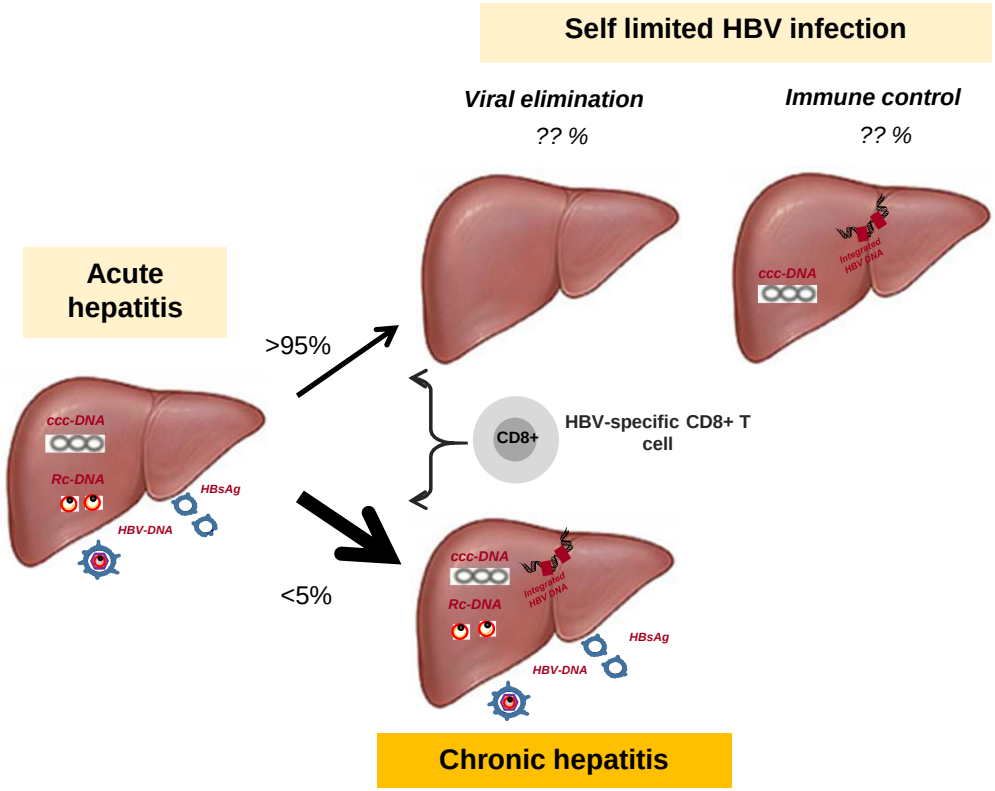
HCV

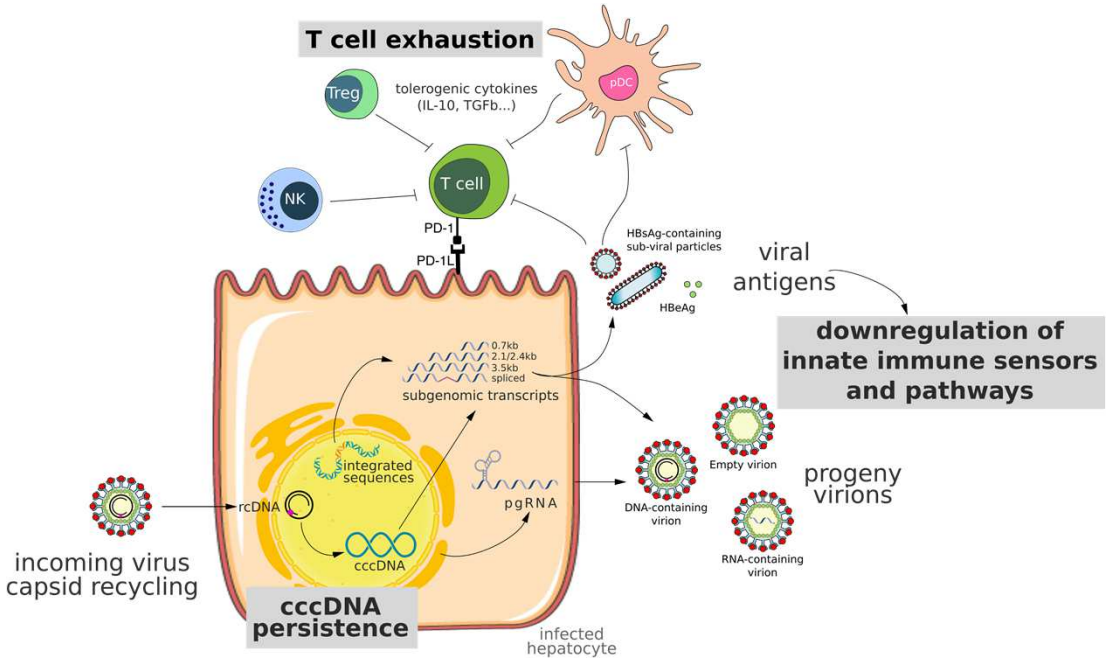


Courtesy of Carlo Ferrari

Thimme, R. et al, *J Exp Med* 2001;194:1395-406

Determinants of HBV Persistence





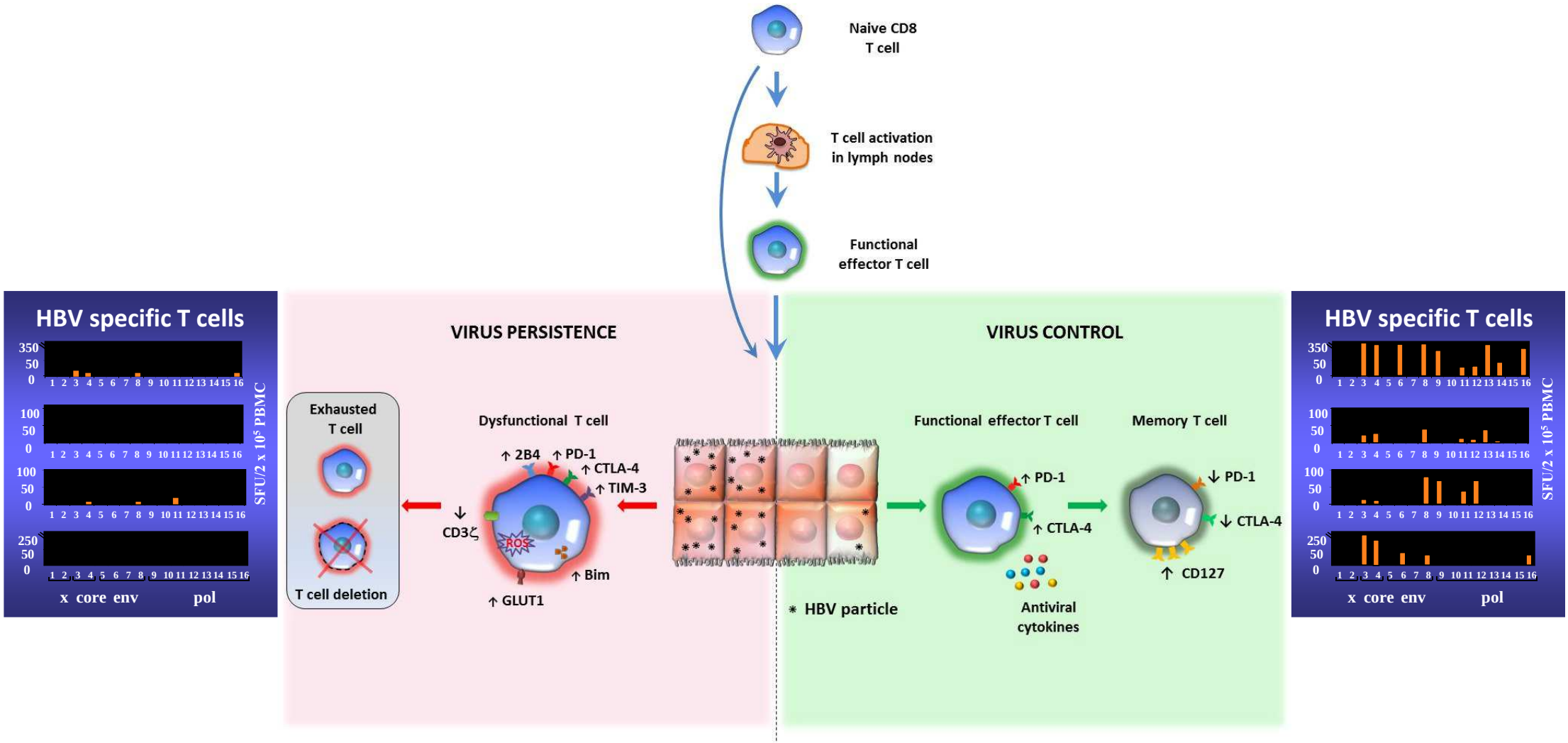
Determinants of HBV persistence

High viral antigen load

Defective innate and adaptive immune responses

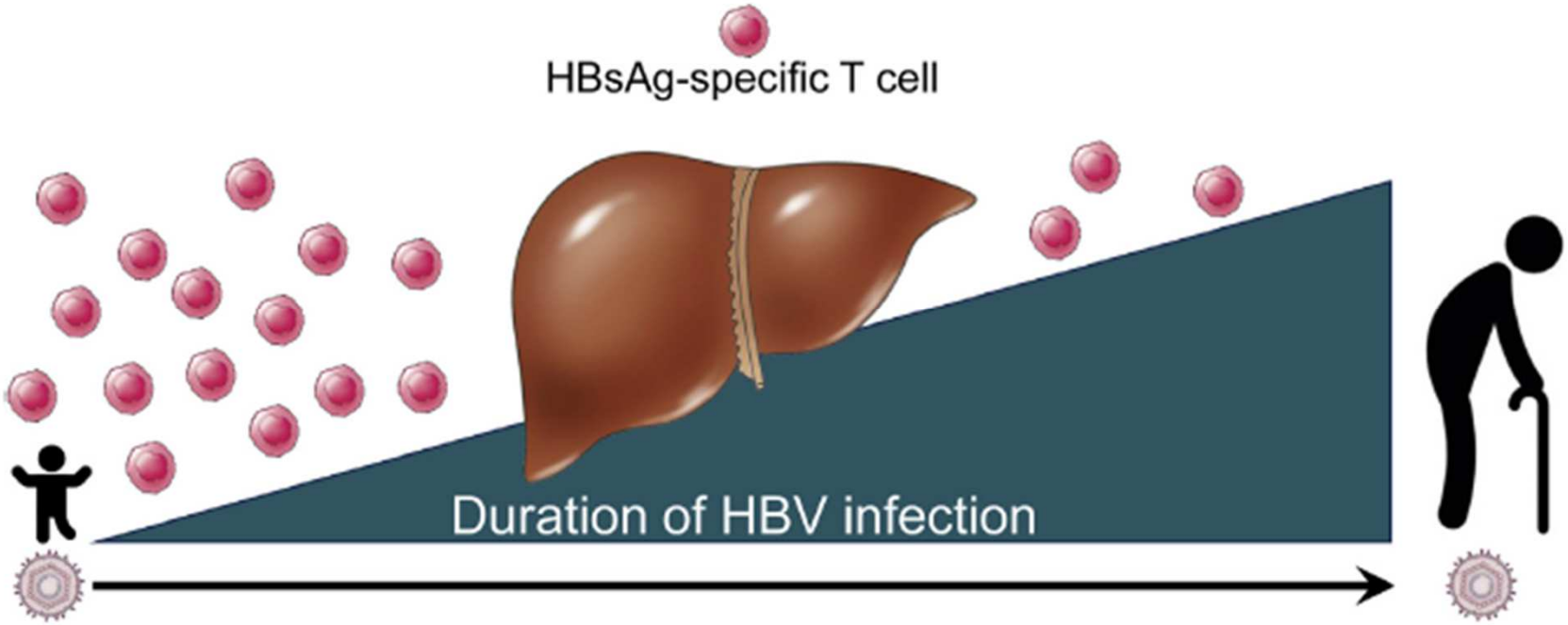
Intrahepatic viral reservoir: long-lived cccDNA

Relationship Between Ag Persistence and Anti-Viral T Cell Responses in the Liver



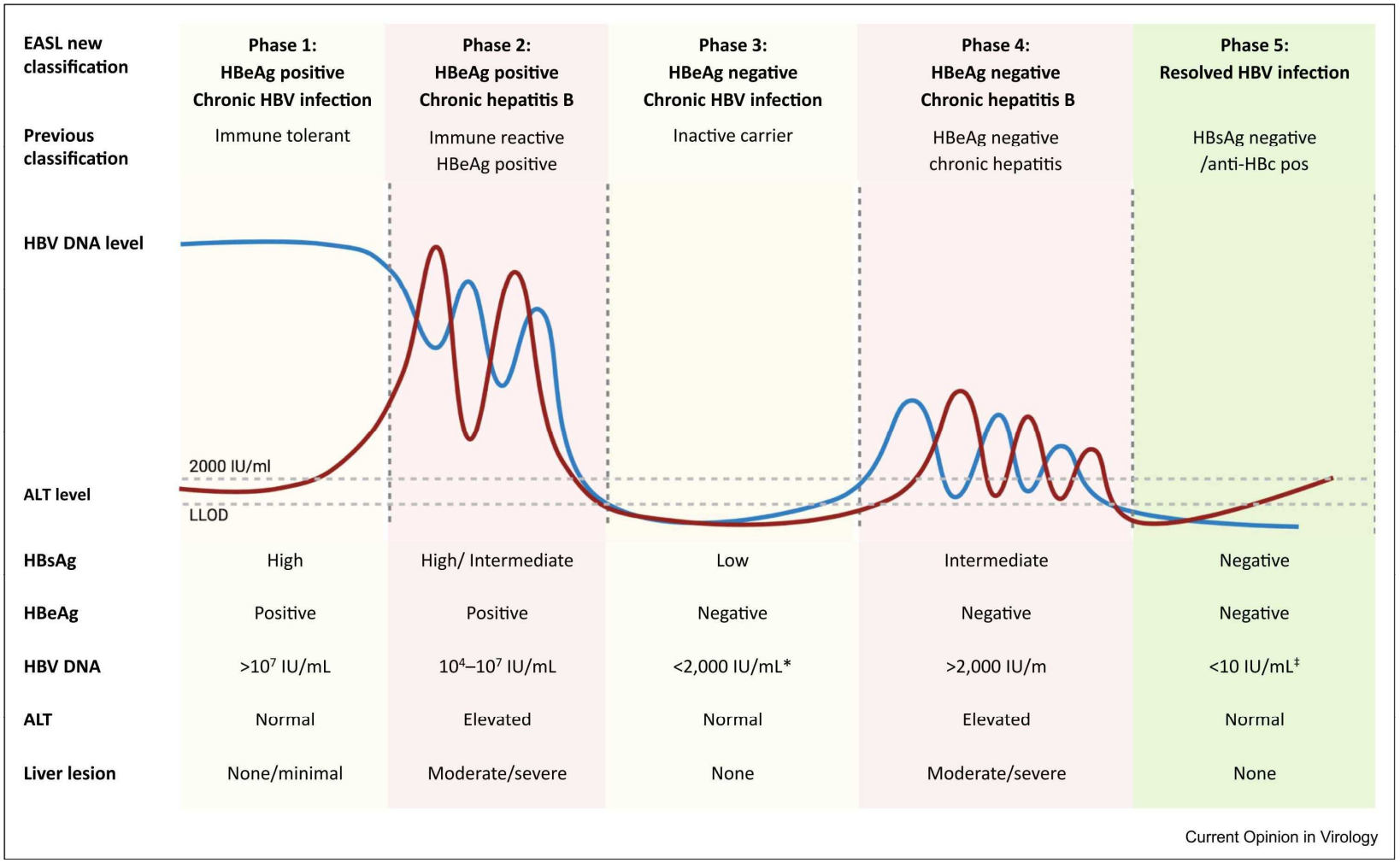
Modified from Fisicaro P, et al. *Front Immunol* 2020;11:849

Duration of HBsAg Exposure, rather than Quantity of HBsAg, Is Associated with Strength of anti-HBV Immune Response



Le Bert N, et al. *Gastroenterology.* 2020;159:652-664

The Natural History of Chronic HBV Infection Is Described by 5 Distinct Phases

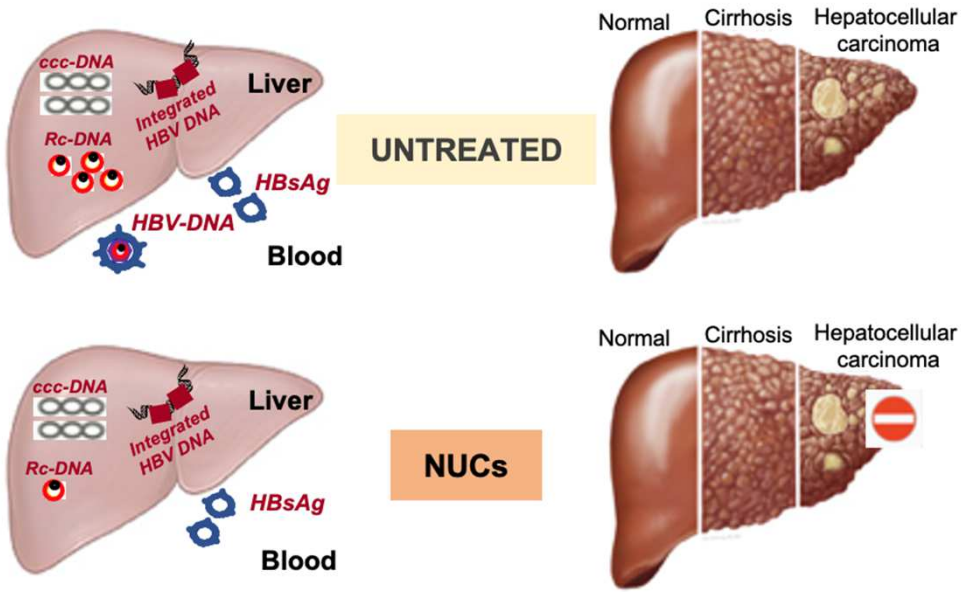


Nasser N, et al. *Curr Opin Virol* 2023 Sep 9;101360.

HBV Cure – Why Do We Need it?

- **PEG-IFN monotherapy** is finite but only effective in a small subgroup of patients and its use is limited due to toxicity
- **HBV nucleos(t)ide analogues** are highly effective and generally well tolerated, but with low rates of HBsAg loss or successful treatment discontinuation

- Need for prolonged / life-long treatment



Courtesy of Massimo Levrero

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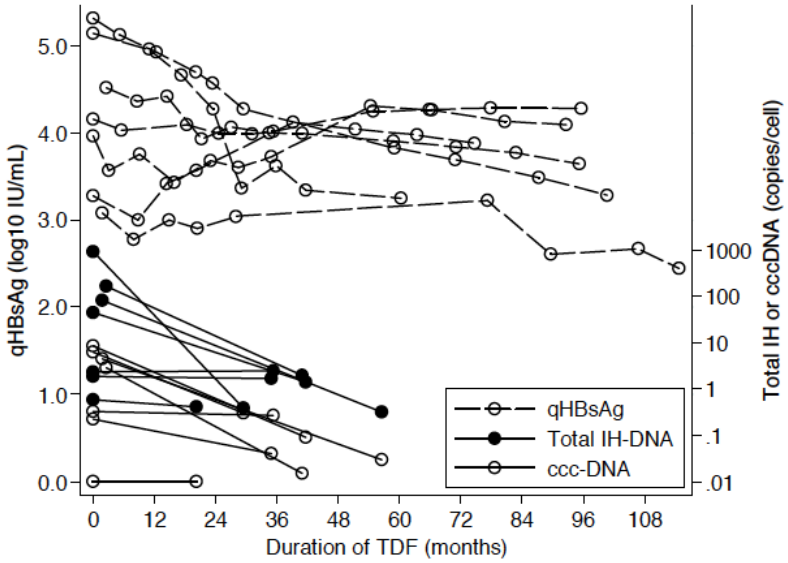
- Need for prolonged / life-long treatment

- Incomplete viral suppression / infectivity
  - **residual intrahepatic viral replication persists**
  - slow decrease of cccDNA pool
  - patient sera with HBV DNA below LLOQ under TDF are infectious



Boyd et al, J Hepatol 2016

Courtesy of Massimo Levrero

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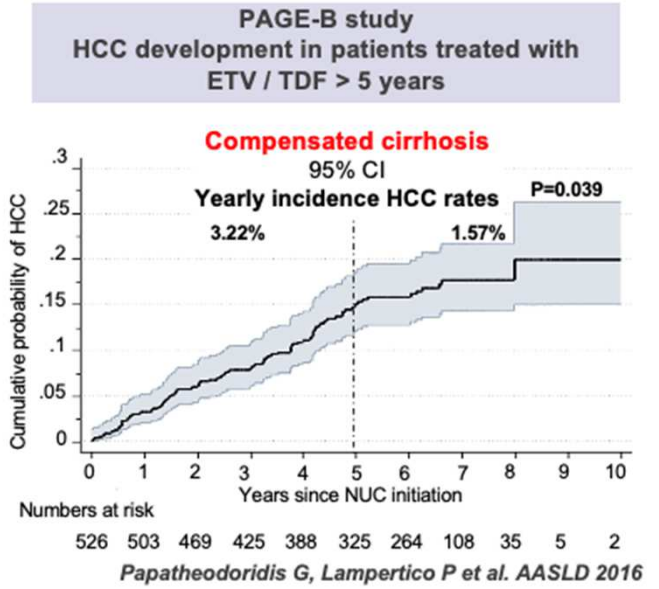
- Need for prolonged / life-long treatment
  - gaps betwen guidelines and health policies

- Incomplete viral suppression / infectivity
  - residual intrahepatic viral replication persists
  - slow decrease of cccDNA pool
  - patient sera with HBV DNA below LLOQ under TDF are infectious

- **Risk of HCC reduced (after 5 yrs) but not eliminated**



HCC risk decreases after 5 years of ETV / TDF treatment
Age ≥50 years and low platelets predict late HCC development

Courtesy of Massimo Levrero

Tests Used in the Management of Patients with HBV Infection

Diagnostic Test	Clinical Interpretation	Notes
HBsAg	Marker of acute and chronic HBV infection	None
qHBsAg	Definition of phase of infection, identifies patients most likely to respond to IFN and likelihood of HBV reactivation	When low, inactive carrier. Predictive of: i) response to IFN; ii) NUC withdrawal; iii) HBsAg loss
Anti-HBs	Marker of immunity (natural or with vaccination)	Marker of HBsAg loss
Anti-HBc	Marker of HBV exposure	When isolated associated with OBI
HBeAg	Associated with high HBV DNA levels, marker of infectivity	HBV flares (changes in levels of ALT and HBV DNA)
Anti-HBe	Associated with lower HBV DNA levels	As above
HBV DNA	Detects HBV infection, used to define phase of infection and need for HBV therapy	Treatment monitoring/reactivation
HBV genotype	Genotypes A–H, determined by detection of specific sequences	Response to PEG/IFN therapy. Useful for epidemiological studies

Guideline Criteria for Treatment of Persons With Chronic HBV Without Cirrhosis

Threshold for Treatment	US Algorithm (2015)[1]	APASL (2016)[2]	EASL (2017)[3]	AASLD (2018)[4]
HBV DNA, IU/mL				
HBeAg positive	≥2000	>20,000	>2000	>20,000
HBeAg negative	≥2000	>2000	>2000	≥2000
ALT	> ULN	>2 x ULN	> ULN	≥2 x ULN
ULN for males	30 IU/L	40 IU/mL	40 IU/L	35 U/L
ULN for females	19 IU/L	40 IU/mL	40 IU/L	25 U/L

- Treat patients with chronic HBV
  - Immune reactive HBeAg positive
  - HBeAg-negative chronic HBV
- All patients with cirrhosis and viremia should be treated

1. Martin. Clin Gastroenterol Hepatol 2015;13:2071. 2. Sarin APASL HBV guidelines. Hepatol Int 2016;10:1.
3. EASL. J Hepatol 2017;67:370. 4. Terrault. Hepatology 2018;67:1560.

Guideline Recommendations: What to Start as Initial HBV Therapy

Treatment	APASL 2016[1]	EASL 2017[2]	AASLD 2018[3]
ETV	Preferred	High barrier to resistance	Preferred
TAF	Not available at time of publication	High barrier to resistance	Preferred
TDF	Preferred	High barrier to resistance	Preferred
PegIFN	Preferred	Only as initial therapy for patients with mild to moderate CHB or selected patients with compensated cirrhosis (and no portal hypertension)	Preferred
Adefovir		Low barrier to resistance	Nonpreferred
Lamivudine		Low barrier to resistance	Nonpreferred
Telbivudine		Low barrier to resistance	Nonpreferred

1. Sarin. Hepatol Int. 2016;10:1. 2. EASL. J Hepatol. 2017;67:370. 3. Terrault. Hepatology. 2018;67:1560.

Slide credit: clinicaloptions.com

2018 AASLD Guidance: Criteria for Selecting ETV vs TAF vs TDF

Comparative Measure	ETV	TAF	TDF
Dose	0.5 mg/day	25 mg/day	300 mg/day
Presence of LAM resistance	Increase dose	Active	Active
Anticipated pregnancy	Pregnancy category C	No human data in pregnancy	Pregnancy category B
Renal disease	Decrease dose if CrCl <50 mL/min	Do not use if CrCl <15 mL/min or if on dialysis*	Decrease dose if CrCl <50 mL/min
Bone disease	Recommended	Recommended	Recommended
HIV coinfection	Only recommended in addition to complete ART regimen	Coformulated ART regimen	Coformulated ART regimen
Cost considerations	Generic available	No generic	Generic available

*By contrast, EASL guidelines recommend **either ETV or TAF in patients receiving hemodialysis**. Since February 2019, TAF prescribing information notes that no dose adjustment is necessary in individuals with CrCl >15 mL/min or in individuals with CrCl <15 mL/min who are receiving hemodialysis.

Terrault. Hepatology. 2018;67:1560. www.aasld.org.

Slide credit: clinicaloptions.com

AASLD and EASL Guidelines: Indications for Choosing ETV or TAF vs TDF

Indications for using ETV or TAF over TDF**:**

- **Aged >60 yr**
- **Bone disease**
  - Chronic steroids or other meds that affect bone
  - **History of fragility fracture**
  - **Osteoporosis**
- **Renal abnormalities**
  - **eGFR <60 mL/min/1.73 m^2**
  - Albuminuria >30 mg or moderate proteinuria
  - Low phosphate (<2.5 mg/dL)
  - Hemodialysis

When to prioritize TAF over ETV:

- Previous nucleoside exposure
  - Lamivudine with or without adefovir resistance
- HIV/HBV coinfection
- No dose adjustment for CrCl ≥15 mL/min

When to prioritize ETV over TAF:

- If less expensive (generic available)
- Dosing guidelines for CrCl <15 mL/min

Terrault. Hepatology. 2018;67:1560. www.aasld.org. EASL. J Hepatol. 2017;67:370.

Slide credit: clinicaloptions.com

EASL and AASLD: On-Therapy Monitoring for People With HBV Treated With Nucleos(t)ide Analogues

- EASL: check HBV DNA every 3-4 mo in the first year, then every 6-12 mo[1]
- EASL: check HBsAg every 12 mo if HBV DNA remains undetectable[1]
  - If HBsAg clears, anti-HBs antibodies should be assessed[1]
- AASLD guidance recommends on-treatment biochemical, serologic, virologic, and histologic assessments[2]
- LFTs every 3-4 mo in first yr, then every 6 mo[1]
- Renal function
  - EASL: bone density study every 3 mo in TDF recipients for first yr, then every 6 mo, if no deterioration[1]
  - AASLD: bone density study at baseline and again during treatment if indicated[2]
- HCC monitoring: ultrasound with or without AFP every 3-6 mo in persons without cirrhosis, depending on presence of any lesions[3]

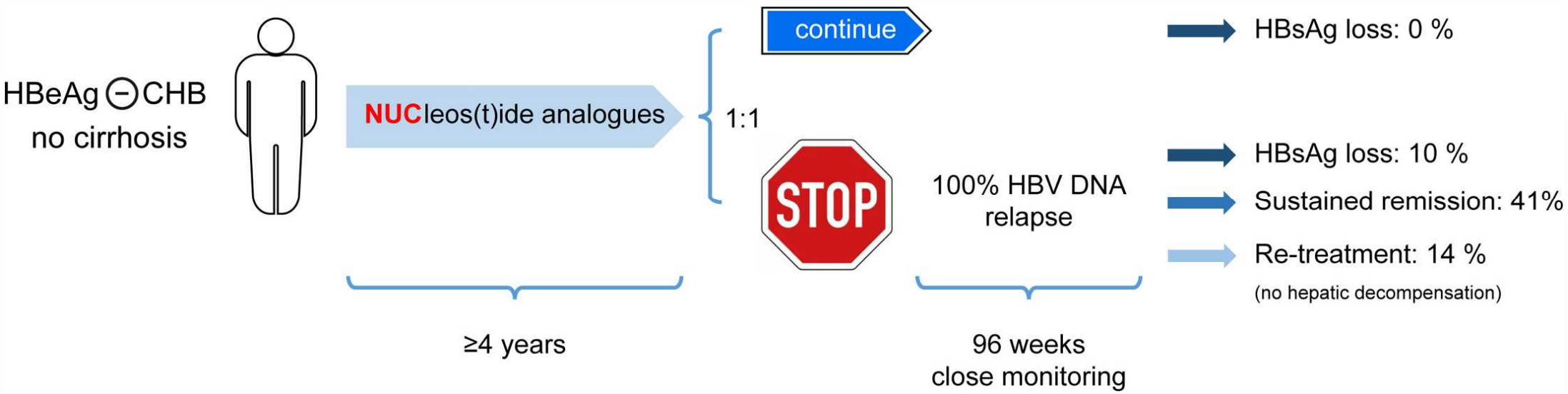
1. EASL. J Hepatol. 2017;67:370. 2. Terrault. Hepatology. 2018;67:1560. 3. Marrero. Hepatology. 2018;68:723.

Slide credit: clinicaloptions.com

2018 AASLD Guidance: Therapy Duration on NAs

- **For most, NA treatment duration is indefinite**
  - HBeAg-positive adults without cirrhosis who seroconvert to anti-HBe on therapy: **discontinue therapy** after a period of treatment consolidation *if this endpoint is met*
  - HBeAg-positive adults with cirrhosis who seroconvert to anti-HBe on NA therapy: **indefinite therapy**, *unless there is a strong competing rationale for treatment discontinuation*
  - HBeAg-negative adults with immune-active CHB: **indefinite therapy**

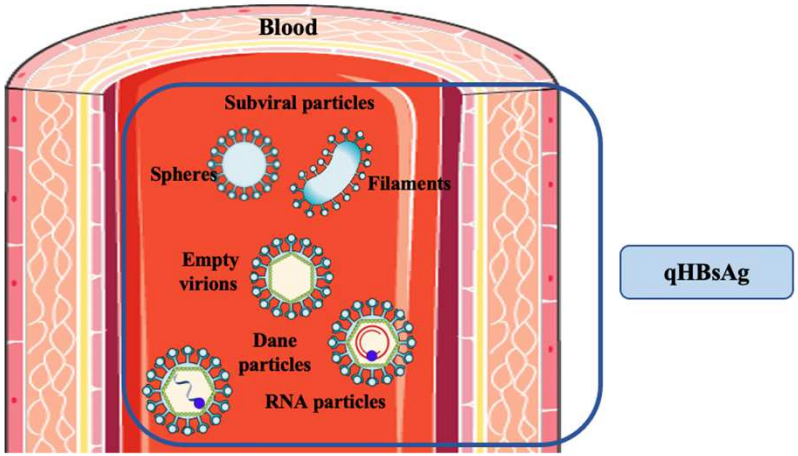
HBsAg Loss and HBsAg Seroconversion after NUC Treatment Discontinuation (HBeAg-)



van Bömmel F, et al. *J Hepatol*. 2023;78:926-936

Diagnosis and on Therapy Monitoring: New Biomarkers

Viral Serum Biomarkers: HBsAg and qHBsAg



qHBsAg correlates with cccDNA levels in HBeAg +ve CHB patients

Thompson et al. Hepatology 2010

limited or no correlation of qHBsAg with cccDNA levels in HBeAg-ve CHB patients, no correlation with 3.5kb/pgRNA levels or cccDNA transcriptional activity

Thompson et al. Hepatology 2010, Testoni et al JHep 2019

qHBsAg : LoD: 0.05 UI/mL
(4.10^7 HBs particules/mL)

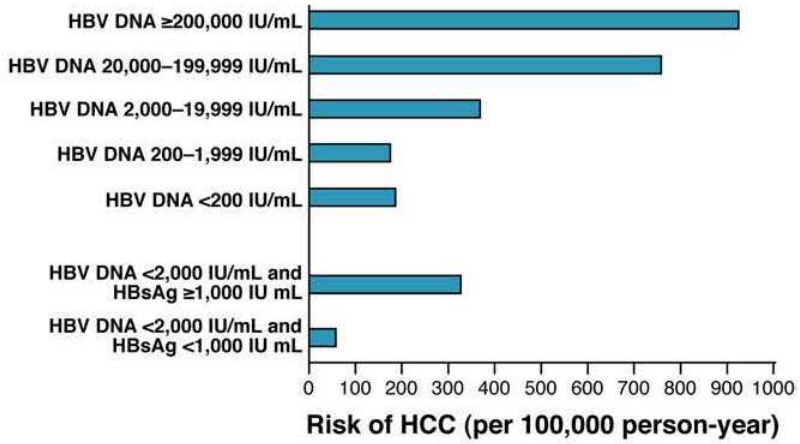
new ultrasensitive qHBsAg : LOD 0.005 UI/mL

HBsAg from both cccDNA (HBeAg +ve patients) and integrated HBV sequences (anti-HBe+ve patients)

Viral Serum Biomarkers: HBV DNA

Suppression of serum HBV DNA levels correlates with significant decrease in HCC risk

ERADICATE-B study



Chan, H L-Y. J Gastro 2012

Risk of HCC remains high for 5-7 years in NUC suppressed cirrhotic patients

Papatheodoridis, JHep 2018

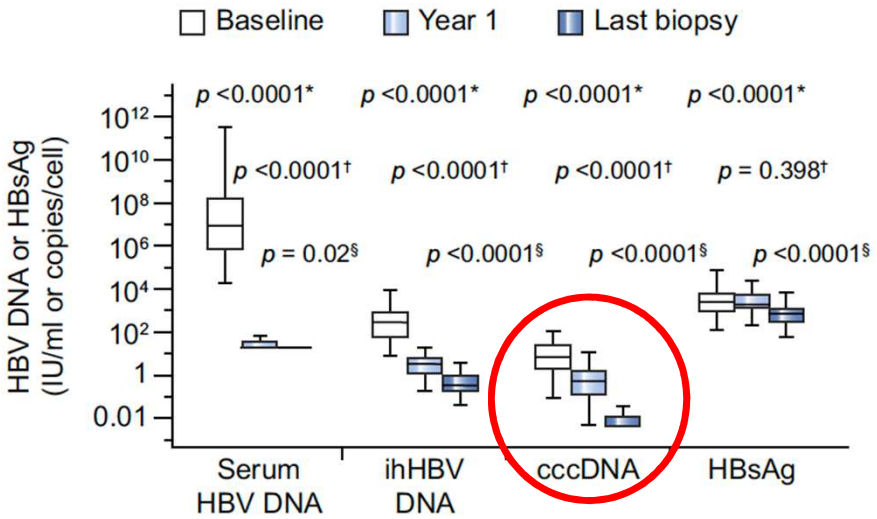
Serum HBV DNA suppression under NUC is not complete

Boyd, JHep 2016

Need for a more sensitive assay?

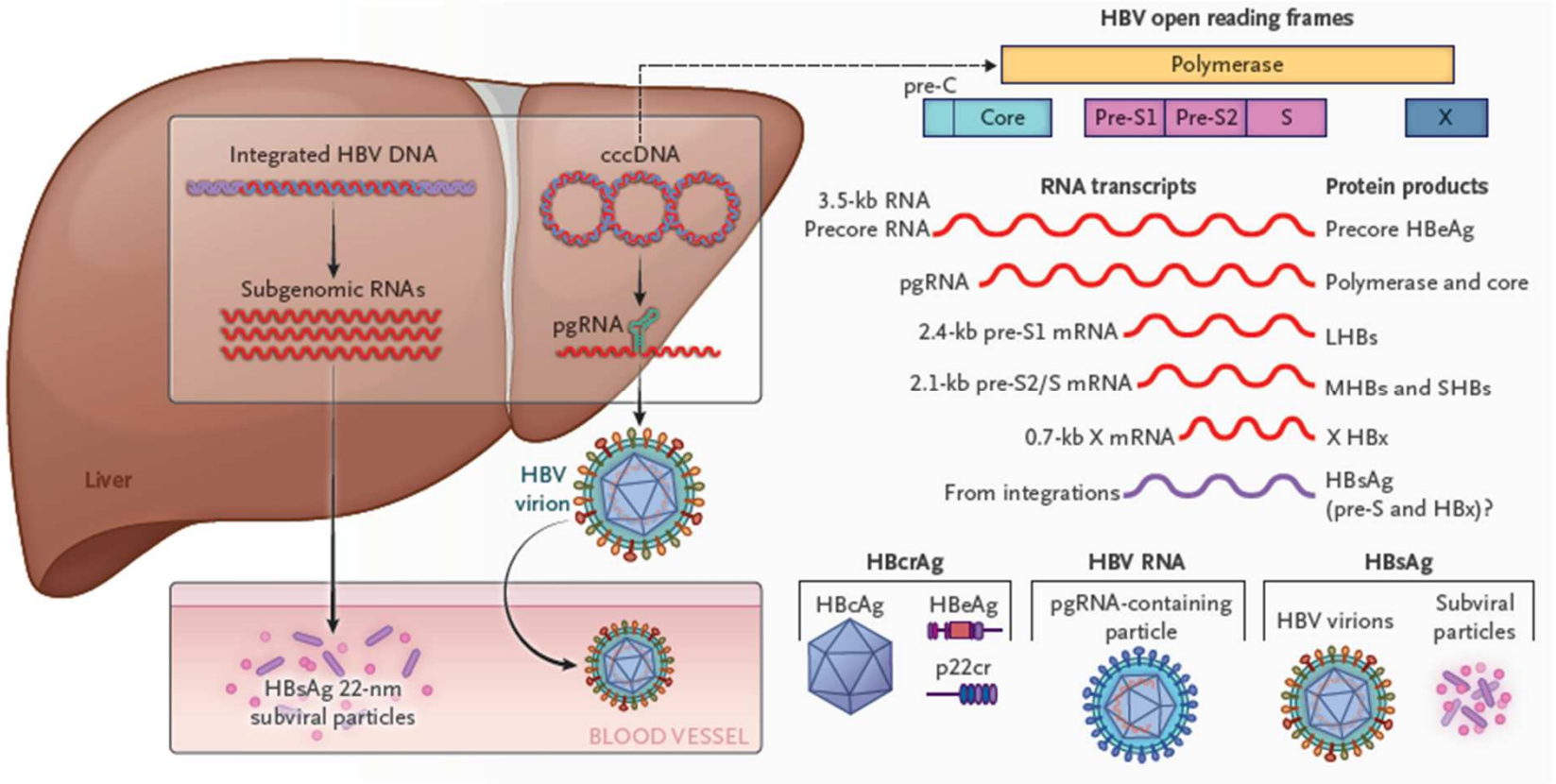
Yuen, LBP30, ILC2020

NUC-induced serum HBV DNA suppression does not eliminate cccDNA



Lai, JHep 2016; Lebossé, Sci Rep in press

HBV Genome Open Reading Frames, RNA Transcripts, Protein Products, and Biomarkers

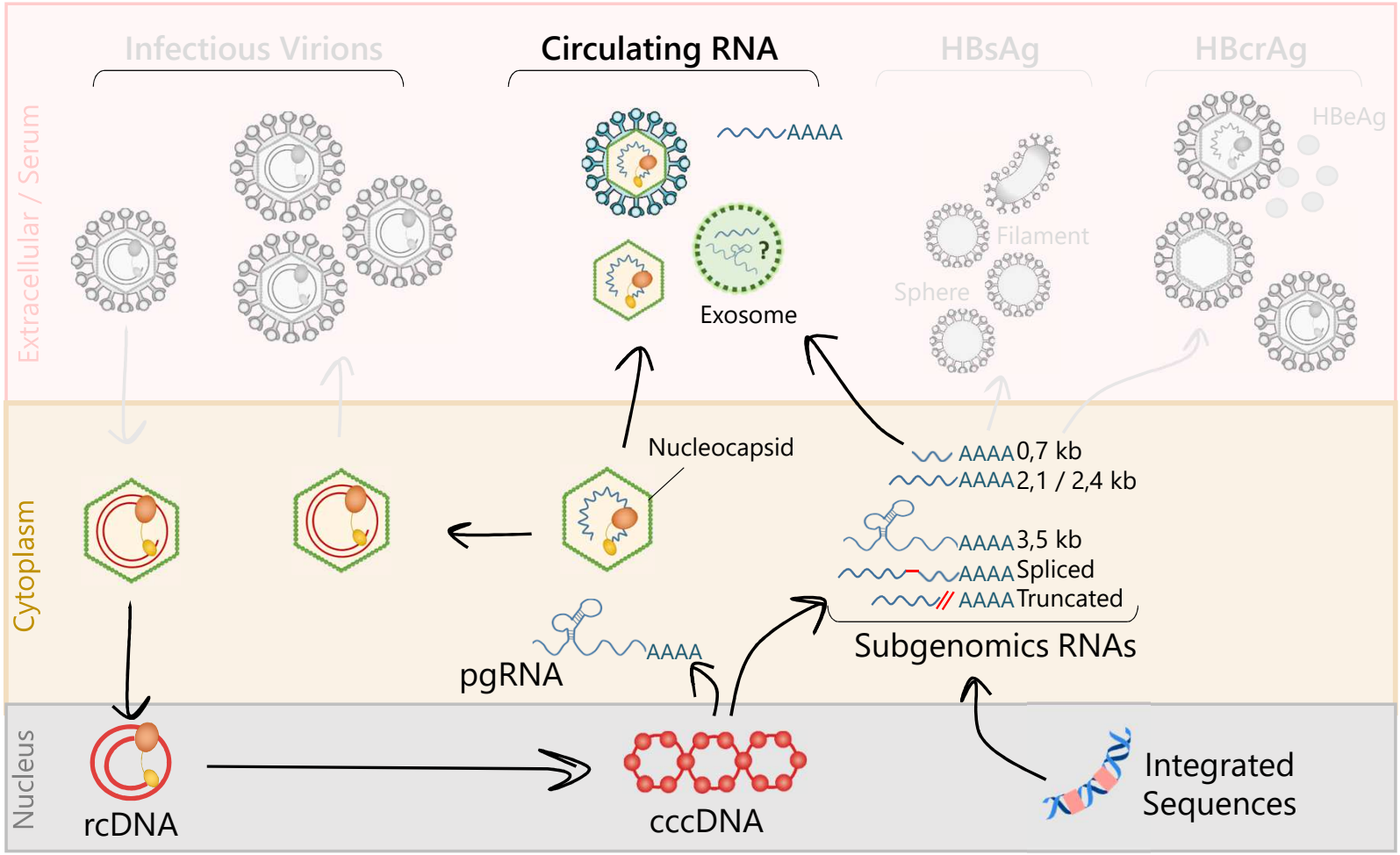


Dusheiko G, Agarwal K, Maini MK. *N Engl J Med* 2023;388:55-69

New Biomarkers for HBV Infection

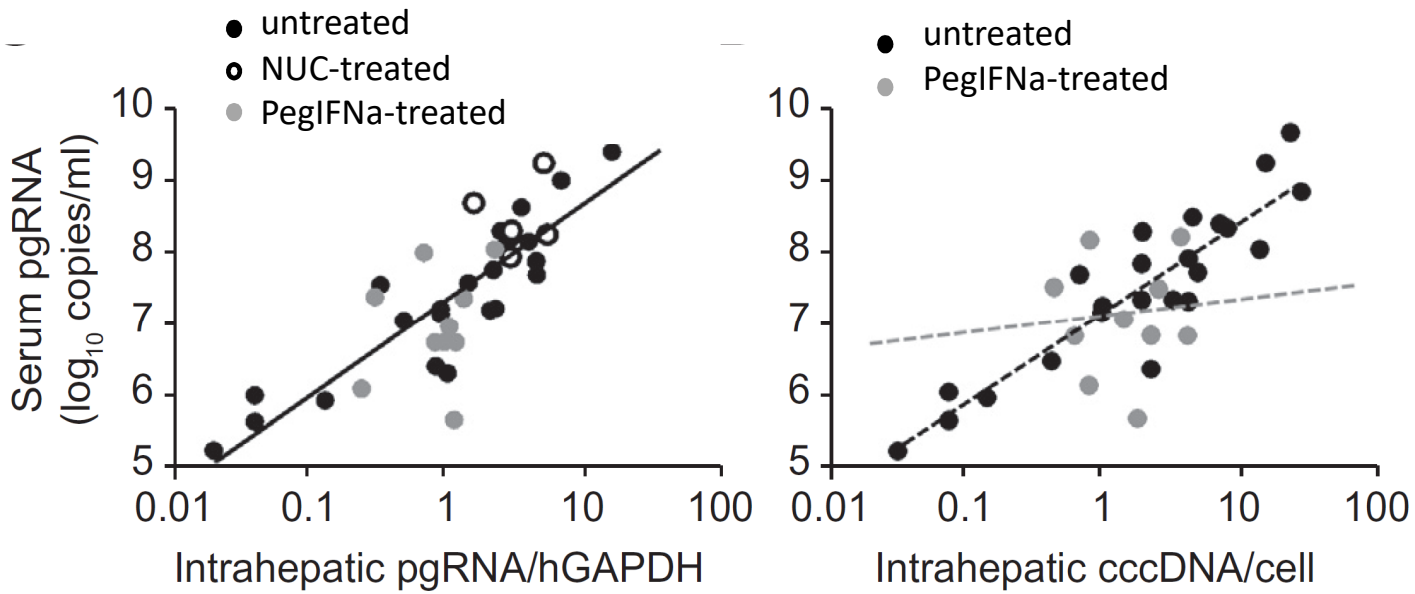
Biomarker	Detection Target	Potential roles in management of patients with chronic HBV infection
Serum HBV RNA	HBV pre-genomic RNA and total serum HBV RNA (variants that cause defects in RNA splicing). Serum levels of pre-genomic RNA indicate transcription of cccDNA	?
HBcrAg	Core antigen associated with circulating virus particles, denatured HBeAg, and p22 core-related protein. Surrogate marker of intrahepatic cccDNA	?

Viral Serum Biomarkers: Circulating HBV RNA



(Adapted from Testoni, Sem Liver Dis 2017)

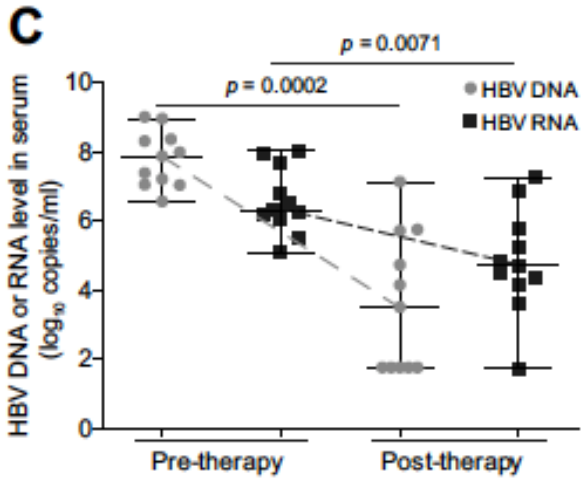
Serum HBV pgRNA as a Clinical Marker for cccDNA Activity

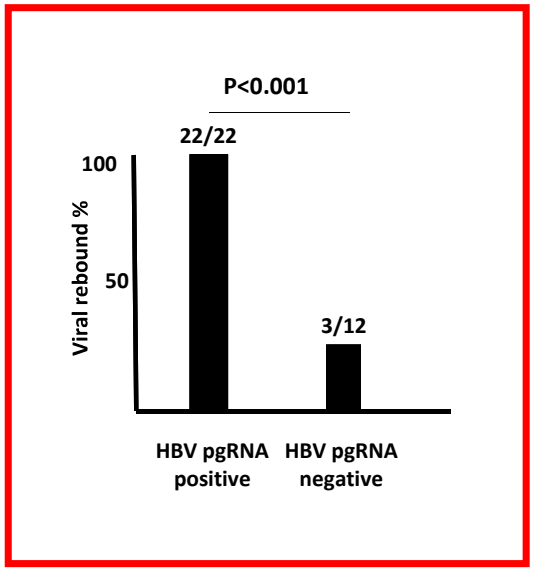


Humanized mouse model infected with HBeAg-positive wild-type HBV

Giersch K et al. *J Hepatol* 2017; 66: 454

Effect of NUC Therapy on Serum HBV pgRNA





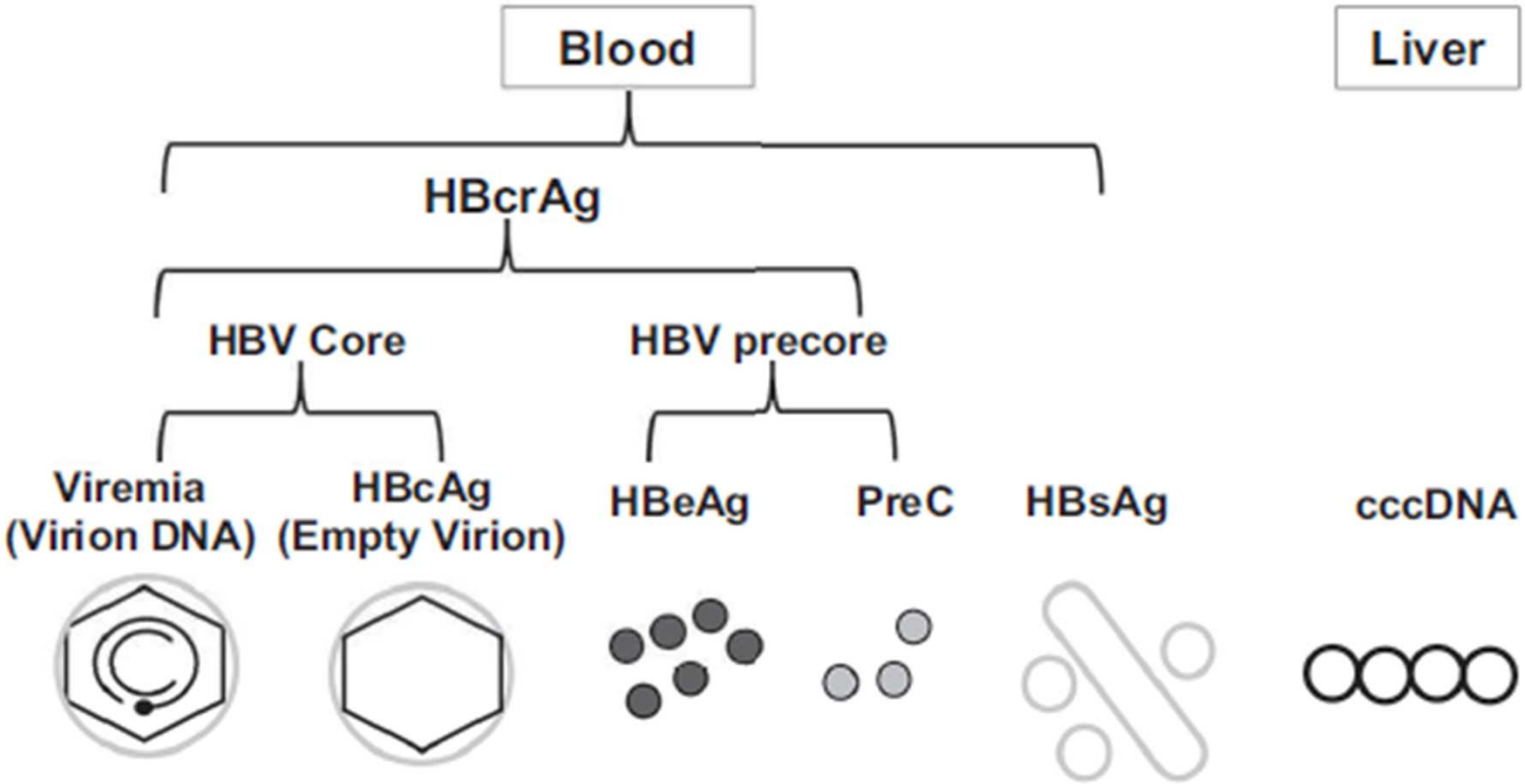
Wang J. et al. *J Hepatol* 2016; 65: 700

Serum HBV RNA as a Clinical Marker

- **Serum HBV RNA could serve as a useful clinical surrogate marker to estimate the intrahepatic activity of cccDNA**
- **HBV RNA measurements could help monitoring the effectiveness of drugs aiming to affect cccDNA transcription and/or pgRNA stability**
- **Could potentially be used as a noninvasive diagnostic biomarker for liver disease activity and progression (in patients receiving NA therapy)**

***Wang J, … Lu F. J Hepatol 2017; 66: 454**

HBcrAg: A New Biomarker of HBV Infection



Hong X, et al. *Hepatology* 2021 Jan 18. doi: 10.1002/hep.31720. Online ahead of print.

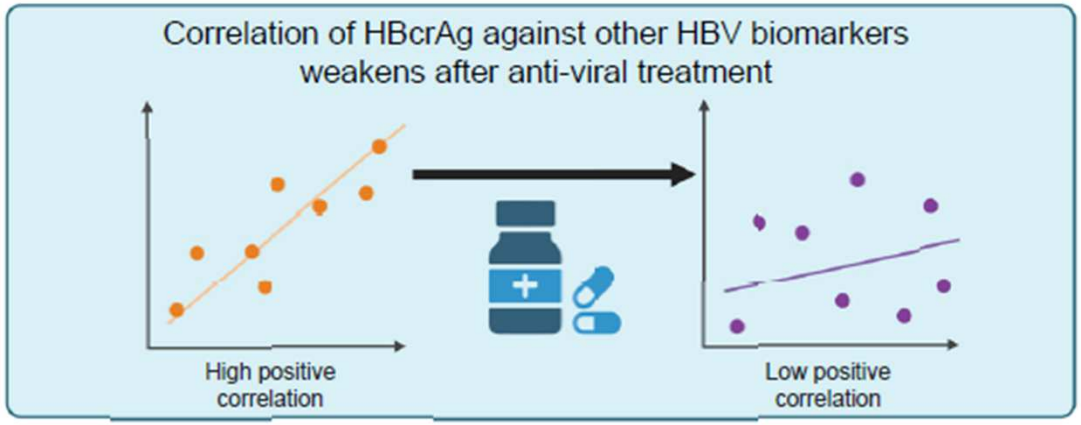
HBcrAg Correlates with cccDNA Transcriptional Activity

HBcrAg is a surrogate marker of both intrahepatic cccDNA and its transcriptional activity that can be 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

Testoni B, et al. *J Hepatol* 2019, 70, 615–625

Using HBcrAg as Predictor of:

- Treatment response
  - 8 studies; median AUROC 0.757
- Relapse after treatment cessation
  - 8 studies; median AUROC 0.688
- HBeAg seroconversion
  - 6 studies; median AUROC 0.860
- HBsAg loss
  - 6 studies; median AUROC 0.645



Modified from Adraneda C., et al. *J Hepatol* 2023;78:731–741

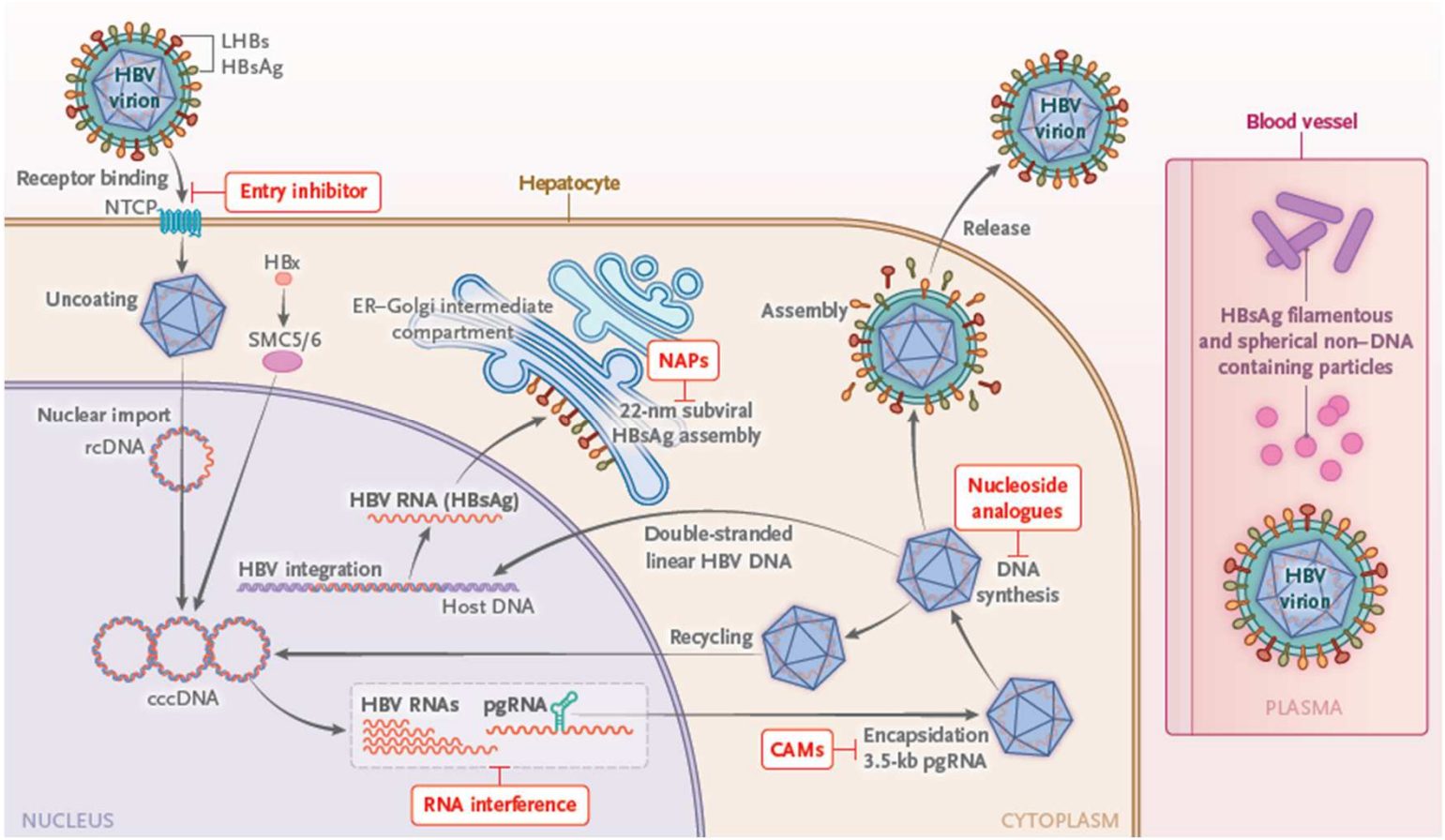
Novel Anti-HBV Drugs

Direct Antiviral Agents Currently in Development

Direct			
Viral entry	Blockage of the NTCP receptor	Bulevirtide	Phase 3[a]
		Hepalatide	Phase 2
	Monoclonal antibody against the pre-S1 domain	VIR-3434	Phase 1
Viral transcription	mRNA disruption by siRNA	JNJ-3989	Phase 2
		AB-729	Phase 2
		RG6346	Phase 2
		VIR-2218	Phase 2
	mRNA disruption by ASO	ALG-125755	Phase 1
		BB-103	Preclinical
		Bepirovirsen	Phase 2
		IONIS-HBVLRx	Phase 2
Core protein	Capsid inhibitor	EDP-514	Phase 2
		Morphothiadin	Phase 2
		RG7907	Phase 2
		Vebicorvir	Phase 2
		JNJ 56136379	Phase 2
		ABI-H3733	Phase 1
		AB-836	Phase 1
		ALG-000184	Phase 1
		QL-007	Phase 1
		VNRX-9945	Phase 1
		ZM-H1505R	Phase 1
		GLP-26	Preclinical
		ABI-4334	Preclinical
cccDNA	Reducing HBX expression	Pevonedistat	Preclinical
		Dicoumarol	Preclinical
HBV polymerase	Prodrugs of nucleotide analogues	Pradefovir	Phase 3
		HS-10234	Phase 3
		NCO-48 fumarate	Phase 1
	Non-chain terminating nucleotide analogue	AT-2173	Phase 2
HBsAg release	NAPs	REP 2139/2165	Phase 2
	STOPS	ALG-010133	Discontinued

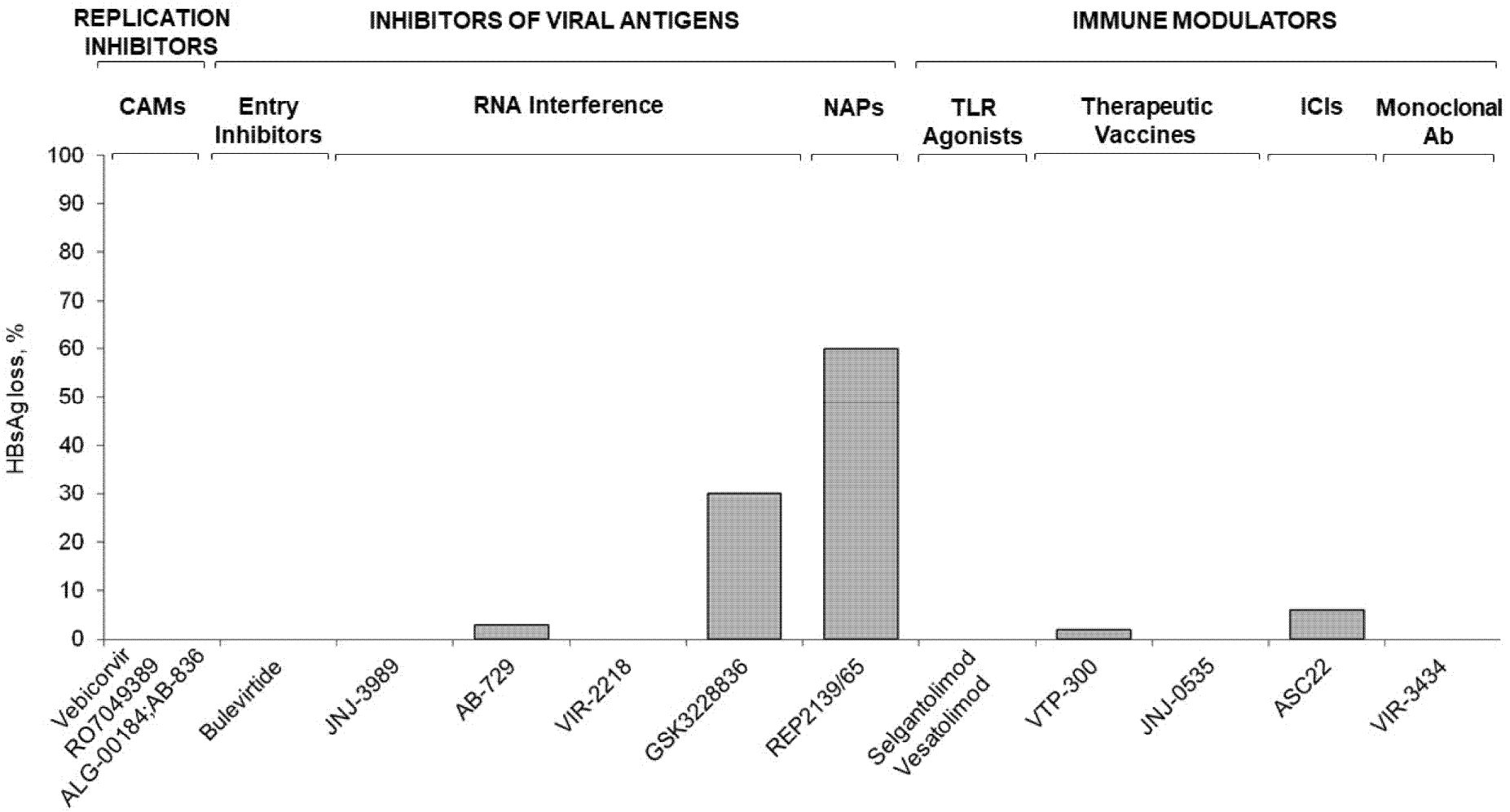
Yardeni D, et al. *Gastroenterology* 2023;164:42-60

HBV Life Cycle and Modes of Action of Novel Antivirals



Dusheiko G, Agarwal K, Maini MK. *N Engl J Med* 2023;388:55-69

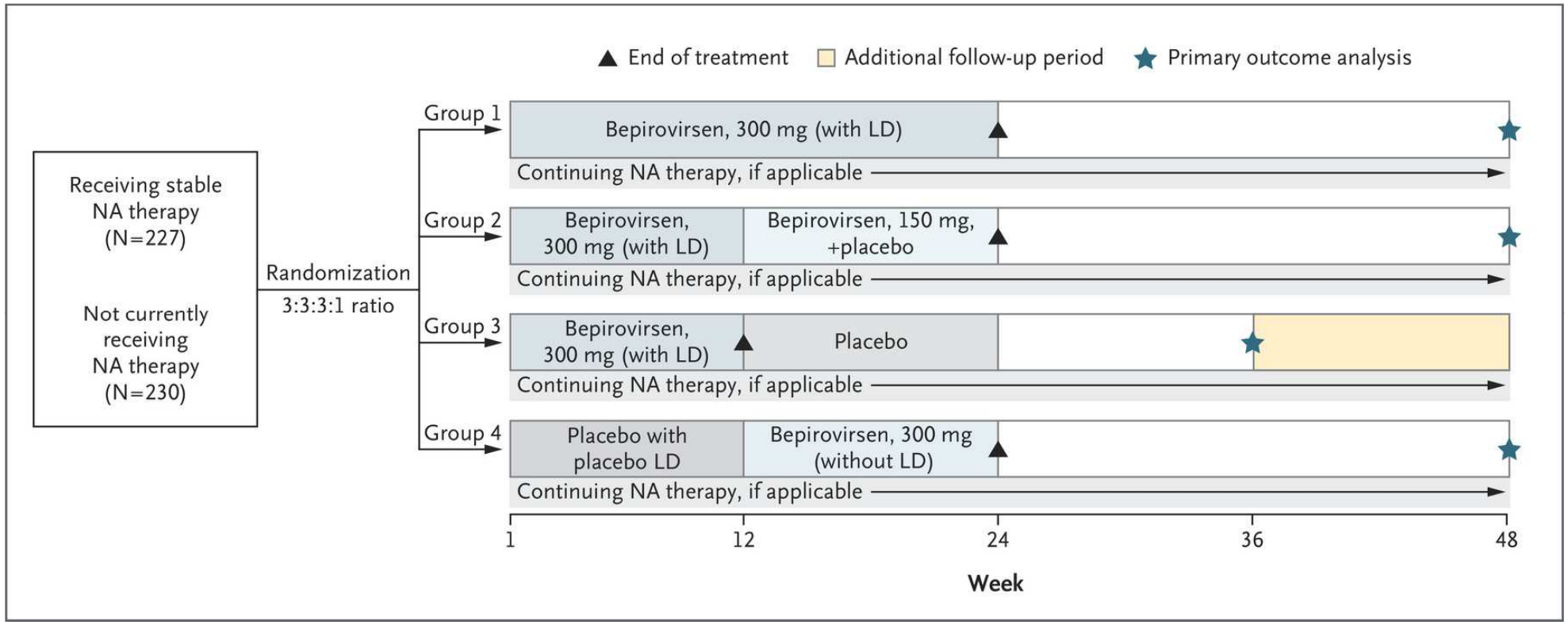
Rates of EOT HBsAg Loss Across the Main Investigational HBV Drugs



Degasperi E, et al. *Viruses* 2022;14:2404

Bepirovirsen in Chronic Hepatitis B Infection: B-Clear Study Design

457 pts (n = 227 stable on NA therapy, n = 230 not on NA therapy)



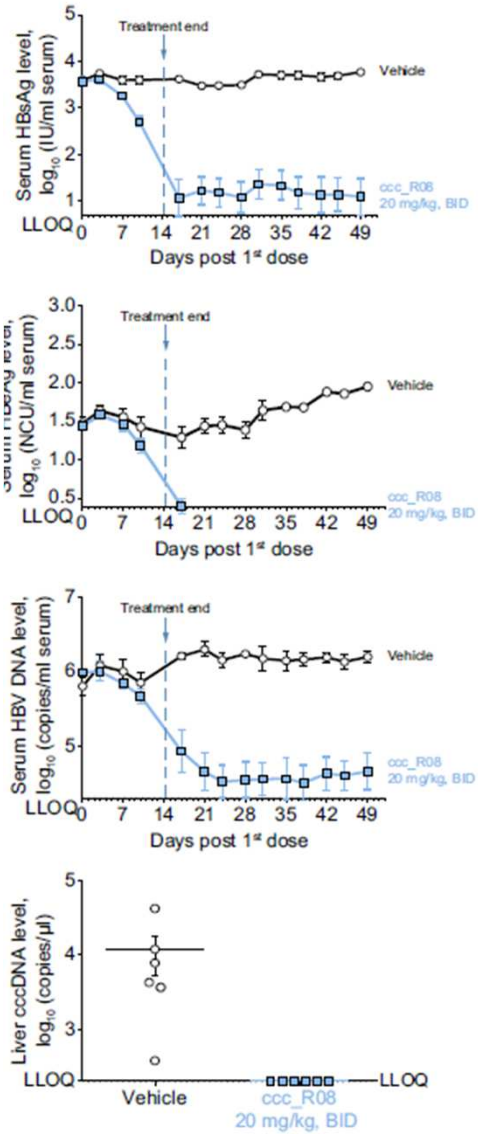
Yuen M-F, et al. *N Engl J Med* 2022;387:1957-1968

B-Clear Trial: Findings

- The primary composite efficacy outcome was an HBsAg level below LLOD and HBV DNA level below LLOQ maintained for 24 weeks after discontinuation of bepirovirsen.
- Bepirovirsen 300 mg per week for 24 weeks (group 1) resulted in 9–10% of participants having HBsAg and HBV DNA loss for 24 weeks after discontinuation of bepirovirsen.
- Results were similar in NA treated and NA untreated pts.
- Baseline HBsAg predicted response, and ROC analysis suggested that HBsAg level of 3000 IU/ml or below at baseline predicted response.
- In HBeAg-negative pts, the primary outcome occurred in 10% and 14% of those receiving NA and in those not receiving NA therapy, respectively.
- In HBeAg-positive pts, the primary outcome occurred only in those receiving NA therapy

Yuen M-F, et al. *N Engl J Med* 2022;387:1957-1968

Anti-HBV Effect of ccc_R08 in a Mouse Model of HBV Infection



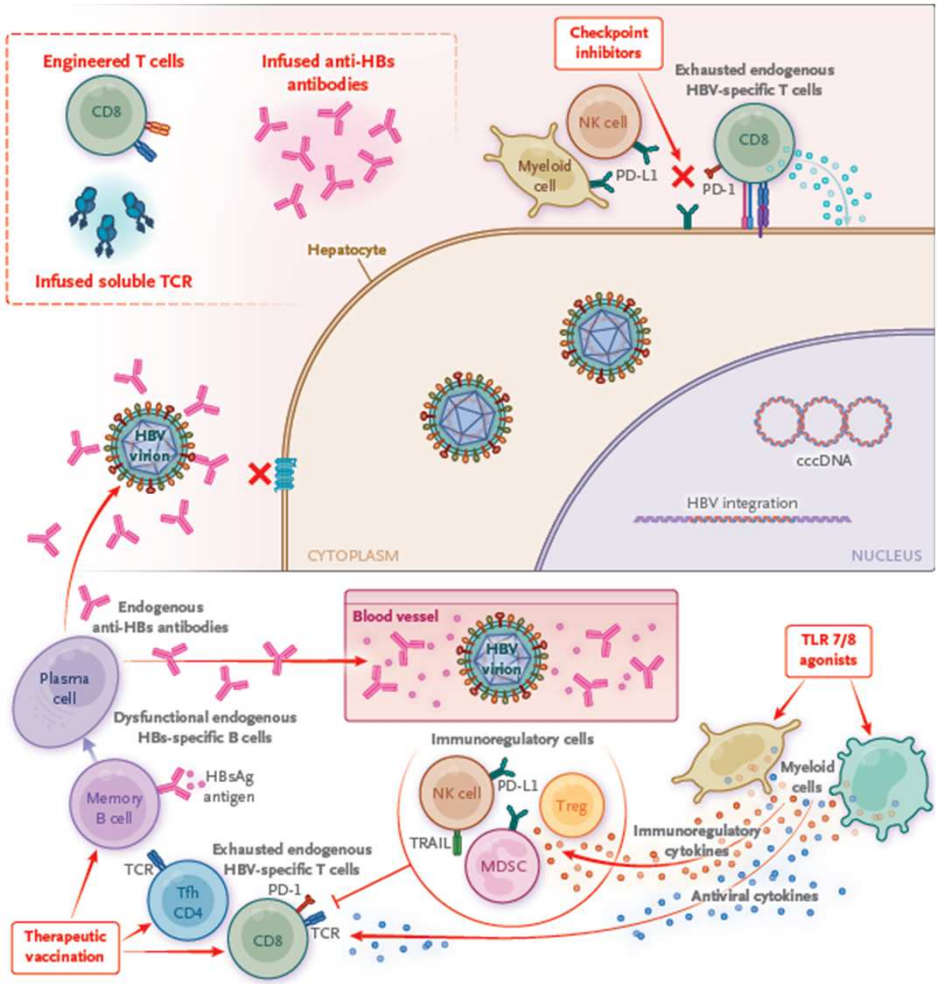
Wang L, et al., *J Hepatol* 2023;78:742-753

Indirect Antiviral Agents Currently in Development

Indirect			
Innate immunity	TLR 7 agonist	Vesatolimod	Phase 2
		RO7020531 (RG7854)	Phase 2
	TLR 8 agonist	GS-9688	Phase 2
		SBT 8230	Preclinical
Adaptive immunity	Checkpoint inhibitor	Nivolumab	Phase 2
		Envafolimab (ASC22)	Phase 2
	Immune mobilizing monoclonal T-cell receptors against virus	IMC-I109V	Phase 2
Therapeutic vaccines	DNA vaccines	GS-4774	Phase 2
		HB-110	Phase 1
		INO-1800/9112	Phase 1
		JNJ-64300535	Phase 1
		MVA-HBV (VTP-300)	Phase 1
		TG1050	Phase 1
		VRON-0200	Preclinical
	T-cell or B-cell epitope vaccine	εPA-44	Phase 2
		FP-02.2 (HepTcell)	Phase 2
	HBV envelope antigen vaccines	NASVAC	Phase 3
		BRII-179	Phase 2
		VVX001	Phase 2

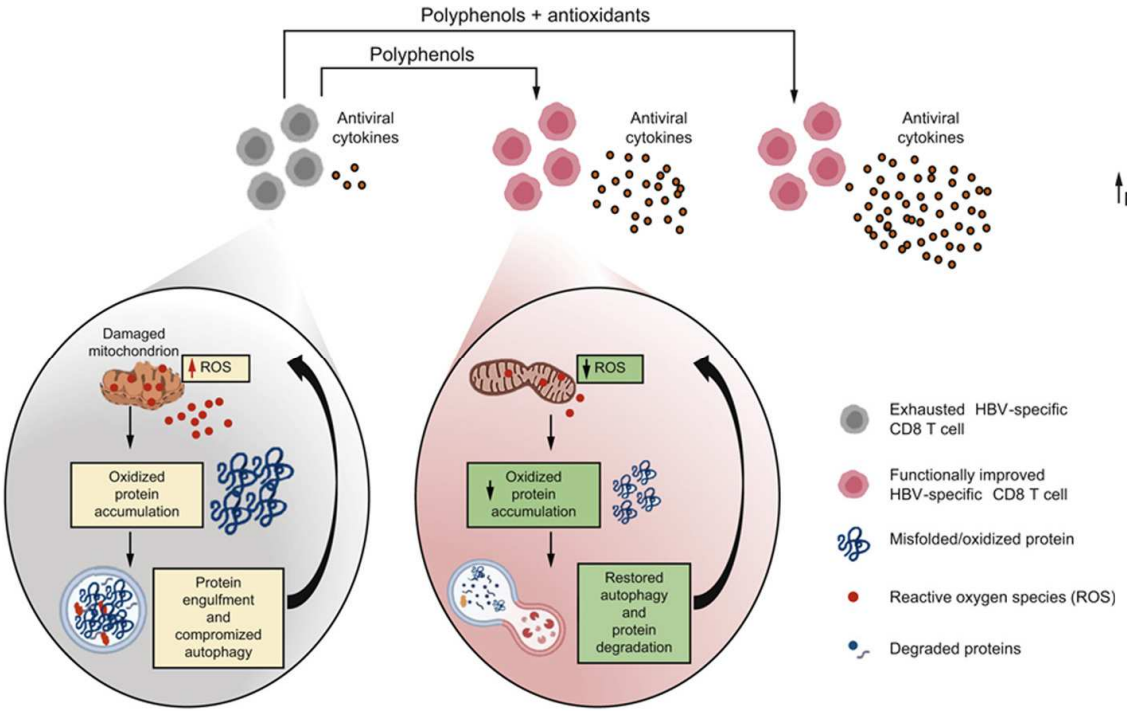
Yardeni D, et al. *Gastroenterology* 2023;164:42-60

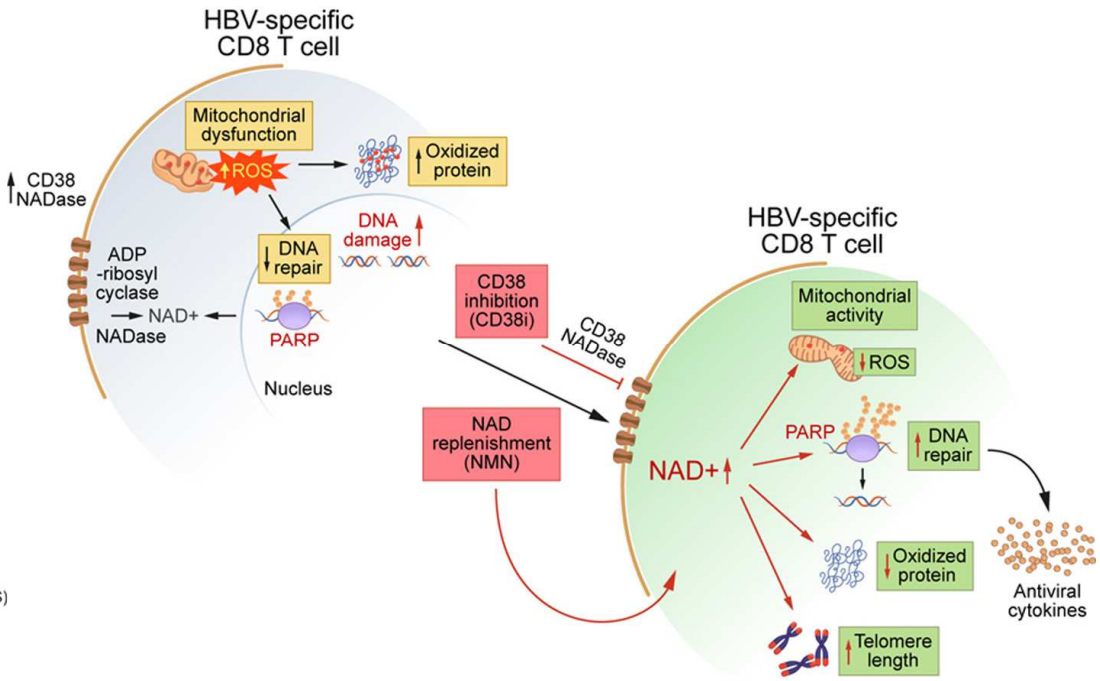
Potential Molecular and Immunotherapeutic Targets



Dusheiko G, Agarwal K, Maini MK. *N Engl J Med* 2023;388:55-69

Exhausted HBV-Specific CD8 T Cells Can Be Functionally Reconstituted





ROS production associated with high DNA damage in HBV-specific CD8 T cells.
NAD depletion maintains and amplifies dysfunction in exhausted HBV-specific T cells.
NAD replenishment can restore T-cell function.

Acerbi G, et al. *J Hepatol* 2021;74:783-793. Montali I, et al. *J Hepatol* 2023;79:50-60

Take Home Messages

- HBV persists indefinitely in the host despite clinical recovery. Factors associated with chronic evolution:
  - High viral Ag load
  - Failure of adaptive immunity (eg CD8 T cell exhaustion)
  - Intrahepatic cccDNA reservoir
- Currently available antivirals reduce incidence of liver decompensation but do not eliminate the risk of HCC
  - Limited effect on cccDNA and integrated HBV DNA
  - No effect on immune dysfunction
  - No reliable biomarkers for NUC discontinuation
- Novel antivirals offer hopes for eradication but the road is long and winding…