Hepatitis B and D
Update on clinical aspects

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PRACTICE GUIDELINE

AASLD Guidelines for Treatment of Chronic Hepatitis B

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Clinical Practice Guidelines

CrossMark

EASL | JOURNAL OF HEPATOLOGY

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

European Association for the Study of the Liver*

Hepatitis B and D
Update on clinical aspects

- Epidemiology
- Treatment
- HBV Cure

HBV Epidemiology - 2017

GLOBAL HEPATITIS REPORT, 2017

68% (16j)*

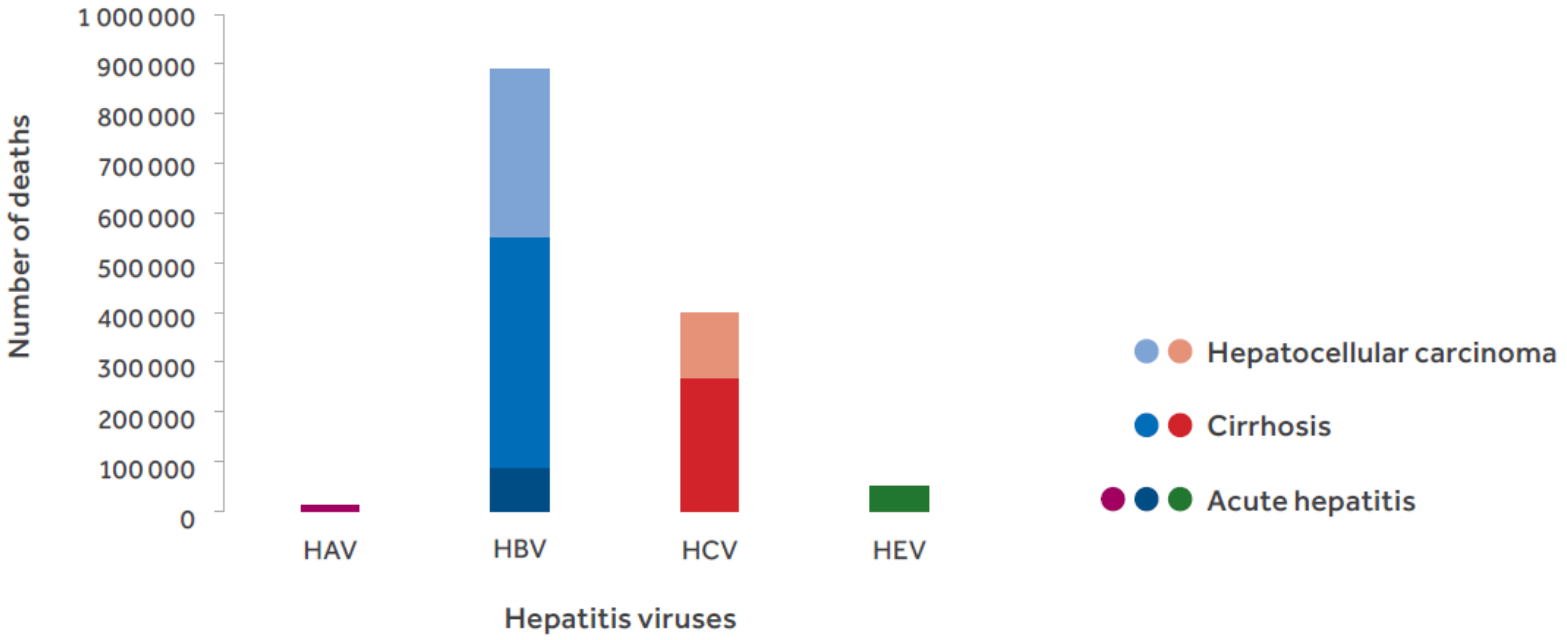
Target areas			Baseli 2015	2020 target	2030 target
Service coverage	Prevention	1 Three-dose hepatitis B vaccine for infants (coverage %)	82%	90%	90%
		2 Prevention of mother-to-child transmission of HBV: hepatitis B birth-dose vaccination or other approaches (coverage %)	38%	50%	90%
		3 Blood and injection safety (coverage %) — Blood safety: donations screened with quality assurance	89%	95%	100%
		3 Blood and injection safety (coverage %) — Injection safety: use of engineered devices	5%	50%	90%
		4 Harm reduction (sterile syringe/needle set distributed per person per year for people who inject drugs [PWID])	20	200	300
	5 Treatment	5a. Diagnosis of HBV and HCV (coverage %)	<5%	30%	90%
		5b. Treatment of HBV and HCV (coverage %)	<1%	5 million (HBV) 3 million (HCV)	80% eligible treated

www.who.int/hepatitis/publications/global-hepatitis-report2017/en/

***Situation analysis www.bag.ch**

HBV Epidemiology - 2017

Fig. 1. Deaths from viral hepatitis, by virus and type of sequelae, 2015:
most viral hepatitis deaths are due to the late complications of HBV and HCV infection



HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus
Source: WHO global health estimates for 2015 published in 2016 (Global Health Estimates 2015: deaths by cause, age, sex, by country and by region, 2000–2015. Geneva: World Health Organization; 2016.)

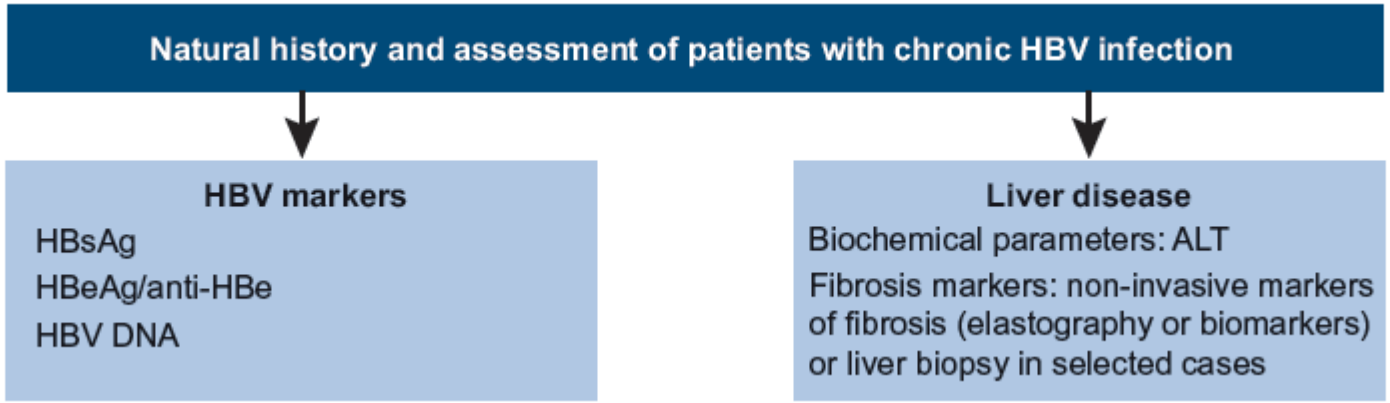
HbsAg pos:	0.5% (44'000)
Anti-HBc:	3.8% (317'000)

Low risk (w/o data from blood donors)

www.who.int/hepatitis/publications/global-hepatitis-report2017/en/

Situation analysis www.bag.ch

HBV disease diagnosis and staging



	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10^7 IU/ml	10^4-10^7 IU/ml	<2,000 IU/ml°°	>2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

EASL CPG Hepatitis B J Hepatol 2017;67:370-98

Indication for treatment

Patients with:

- HBeAg pos or neg CHB, defined by:
  - HBV-DNA>2'000IU/ml
  - ALT>ULN and/or
  - Moderate necroinflammantion or fibrosis should be treated
- Comp. or decomp. cirrhosis with any detectable HBV-DNA and regardless of ALT need treatment
- HBV-DNA>20'000IU/ml and ALT>2xULN should start treatment
- HBeAg chronic HBV infection may be treated, if>30yrs
- HBeAg pos or neg CHB infection and family history of HCC or cirrhosis and extrahepatic manifestations can be treated

EASL CPG J Hepatol 2017; 67:370-398

Treatment Goals

	Viral suppression
Clincial scenario	HBe-Ag neg. HBV infection under treatment
HBsAG	Positive
Anti-HBs	Negative
HBV-DNA	Low level or ot detected
Hepatic cccDNA transscription	Detected Low level
Integrated HBV DNA	Detected
Liver damage	Inactive
Risk of HCC	Lower risk vs. untreated

Lok et al Hepatology 2017;doi 10.1002/hep.29323
Durantel et al J Hepatol 2016;64:S117-131

Treatment Options HBV

Interferon	Nucleoside	Nucleotide
PEG-INF2a	Lamivudine	Adefovir
	Entecavir	Tenofovir DPV
	Telbivudine	Tenofovir TAF

	Pegylated interferon	NUCs
Advantages	• Finite duration • Absence of resistance • Higher rates of HBeAg and HBs seroconversion	• Potent antiviral effect • Good tolerance • Oral administration
Disadvantages	• Moderate antiviral effect • Poor tolerance • Subcutaneous injections	• Indefinite duration • Risk of resistance • Lower rates of HBeAg and HBs seroconversion

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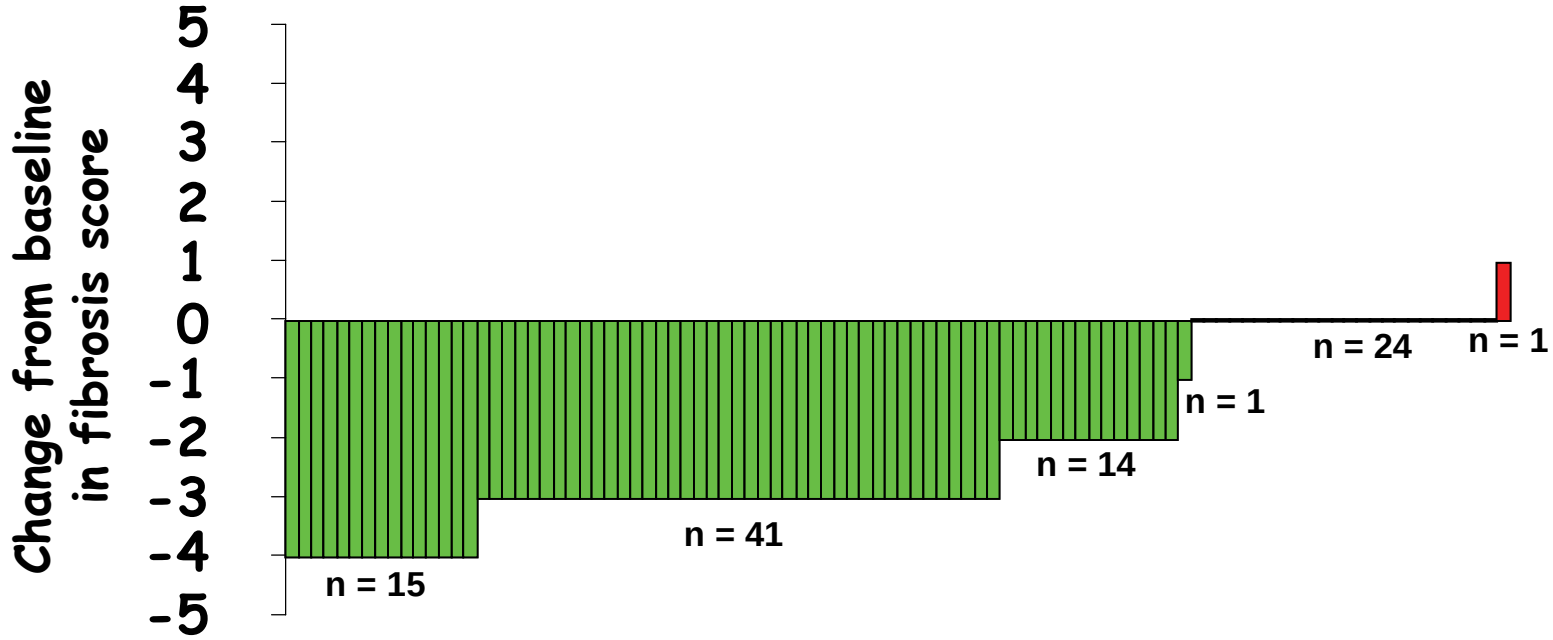
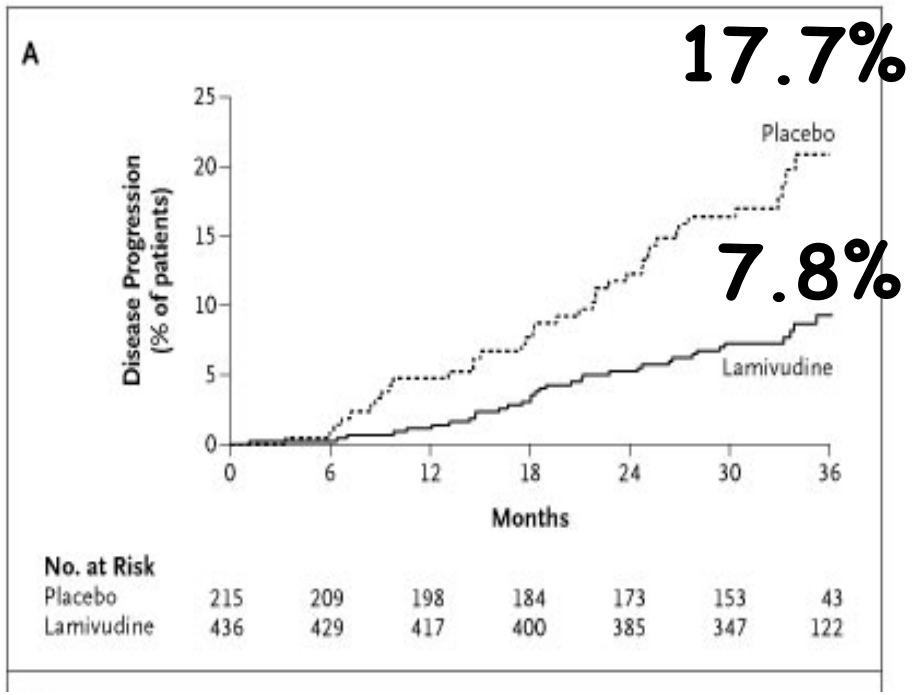
HBV-Elimination Improves Outcome

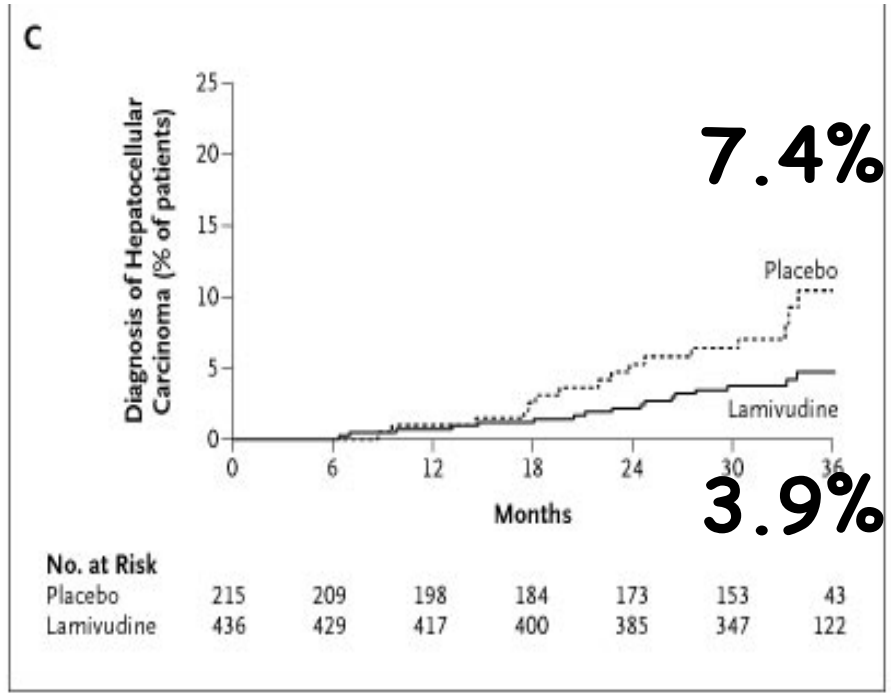


- 96 patients with cirrhosis (Ishak fibrosis score≥5) had paired BL and year 5 biopsies
- 74% (n=71) of patients had cirrhosis reversed (Ishak fibrosis score <5) at year 5

Marcellin et al. Lancet. 2013;381:468-75

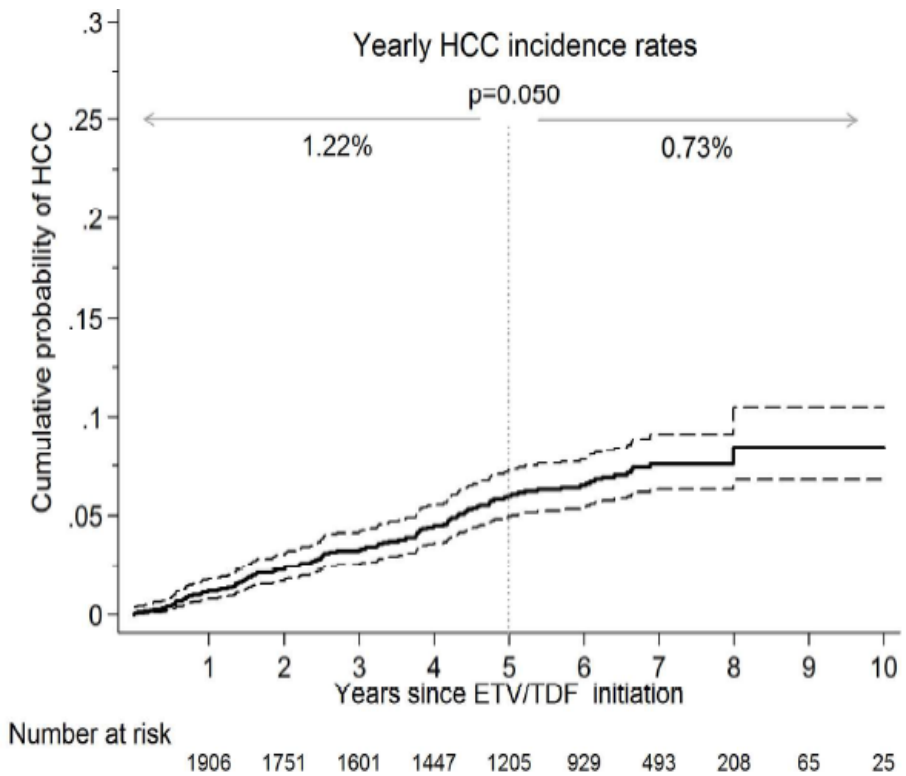
HBV-Elimination Improves Outcome

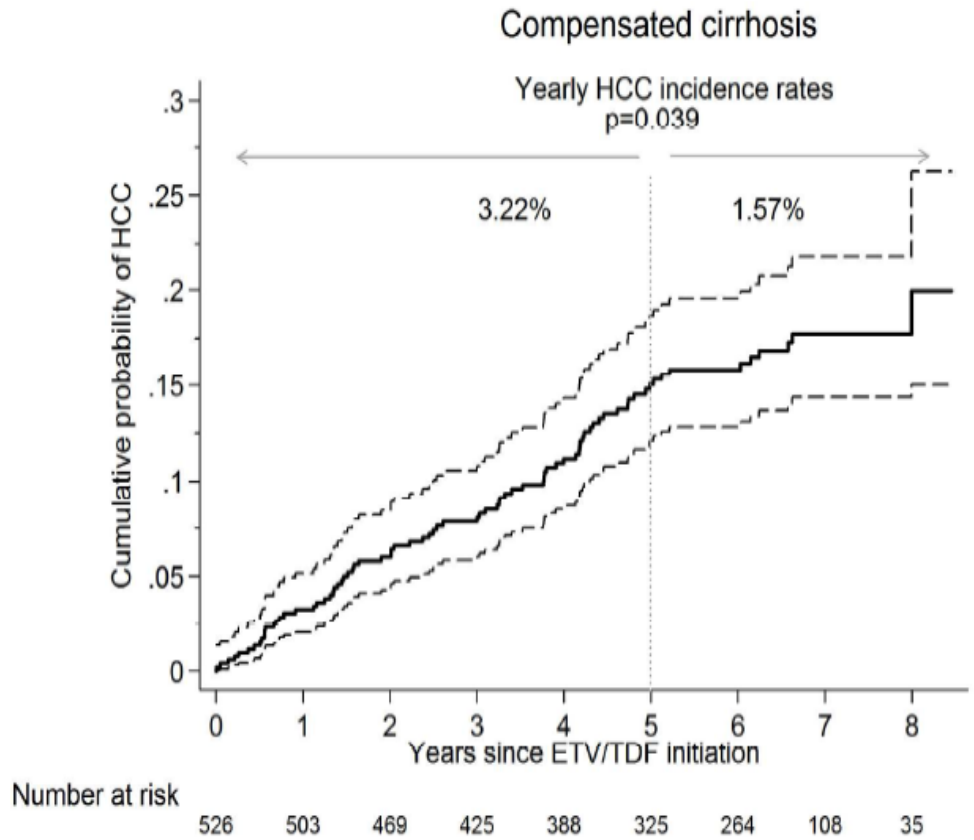




Liaw, Y.-F. et al. N Engl J Med 2004;351:1521-153

HCC risk over time





Risk factors for HCC after year 5: Age > 50yrs at onset of therapy
lower Tc and
stiffness > 12kPa at year 5

Papatheodoridis et al Hepatology 2017;66:1444-53

Stopping NUC treatment

- NAs should be discontinued after confirmed HBsAg loss, with or without anti-HBs seroconversion.
- NAs can be discontinued in non-cirrhotic HBeAg positive with stable HBeAg seroconversion and undetectable HBV DNA and who complete at least 12 months of consolidation therapy. Close post-NA monitoring is warranted
- Discontinuation of NAs in selected non-cirrhotic HBeAg-negative patients who have achieved longterm (P3 years) virological suppression under NA(s) may be considered if close post-NA monitoring can be guaranteed

Papatheodoridis et al Hepatology 2016;63:1481-92

Treatment Goals

	Viral suppression	Partial Cure	Realistic functional cure
Clincial scenario	HBe-Ag neg. HBV infection under treatment	HBe-Ag neg. HBV infection off treatment	Chronic HBV with HBsAg loss
HBsAG	Positive	Positive	Negative
Anti-HBs	Negative	Negative	Negative/positive
HBV-DNA	Low level or ot detected	Not detected	Not detected
Hepatic cccDNA transscription	Detected Low level	Detected Low level	Detected Not active
Integrated HBV DNA	Detected	Detected	Detected
Liver damage	Inactive	Inactive, fibrosis regresses over times	Inactive, fibrosis regresses of time
Risk of HCC	Lower risk vs. untreated	Lower risk vs. untreated	Declines with time

Lok et al Hepatology 2017;doi 10.1002/hep.29323
Durantel et al J Hepatol 2016;64:S117-131

Treatment Goals

	Viral suppression	Partial Cure	Realistic functional cure	Idealistic functional cure	Complete sterilizing cure
Clincial scenario	HBe-Ag neg. HBV infection under treatment	HBe-Ag neg. HBV infection off treatment	Chronic HBV with HBsAg loss	Recovery after acute HBV	Never infected
HBsAG	Positive	Positive	Negative	Negative	Negative
Anti-HBs	Negative	Negative	Negative/positive	Positive	Negative
HBV-DNA	Low level or ot detected	Not detected	Not detected	Not detected	Not detected
Hepatic cccDNA transscription	Detected Low level	Detected Low level	Detected Not active	Detected Not active	Not detected
Integrated HBV DNA	Detected	Detected	Detected	Detected?	Not detected
Liver damage	Inactive	Inactive, fibrosis regresses over times	Inactive, fibrosis regresses of time	None	None
Risk of HCC	Lower risk vs. untreated	Lower risk vs. untreated	Declines with time	Not increased	Not increased

Lok et al Hepatology 2017;doi 10.1002/hep.29323
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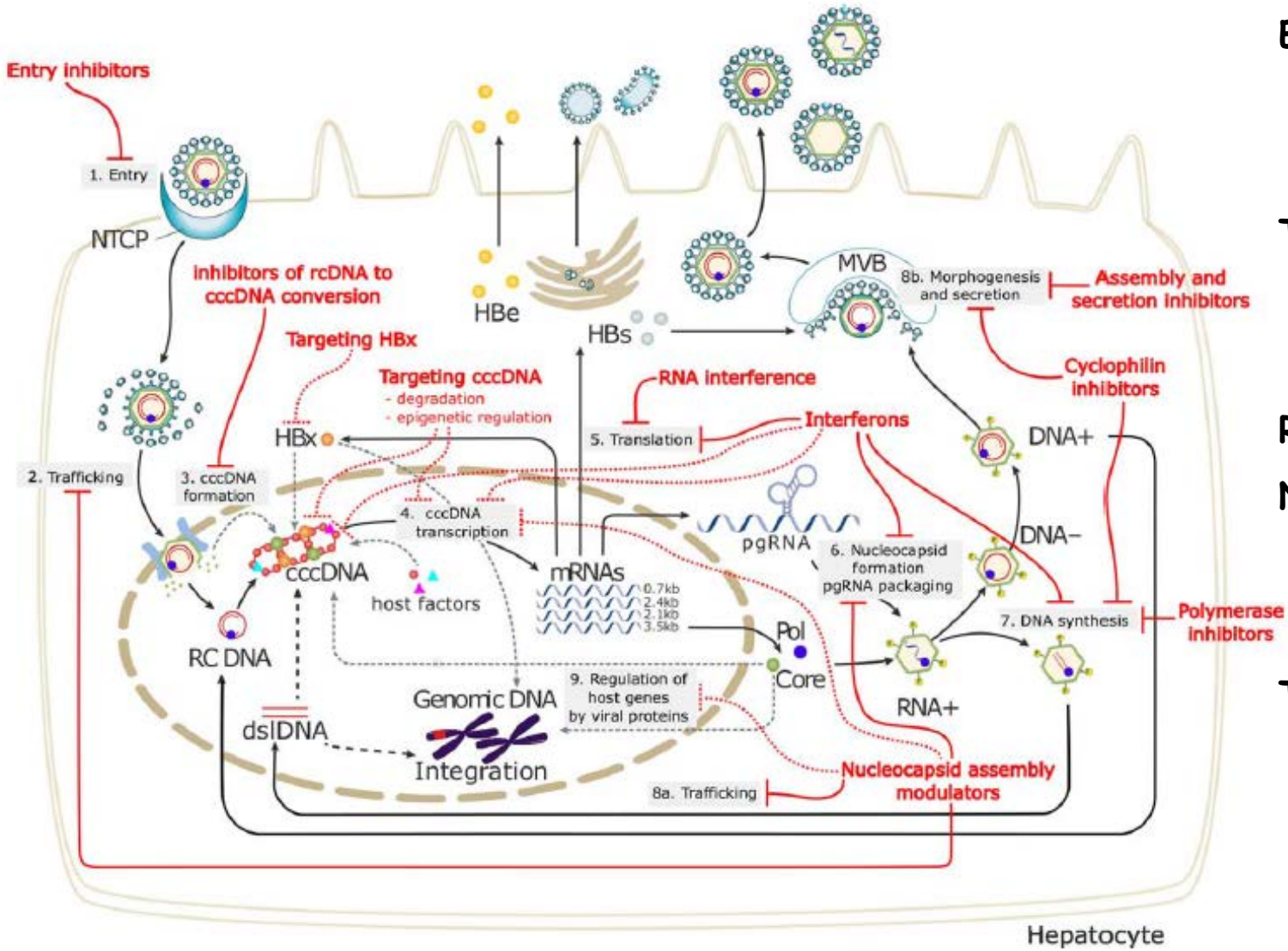
Approaches to HBV Cure



Entry Inhibitors:

- HBs Antibodies
- Irreversible NTCP inhibitors (Myrcludex B)

Targeting cccDNA and HBx

- Damage and Destruction
- Functional Silencing

RNA interference

Nucleocapsid Assembly modulators

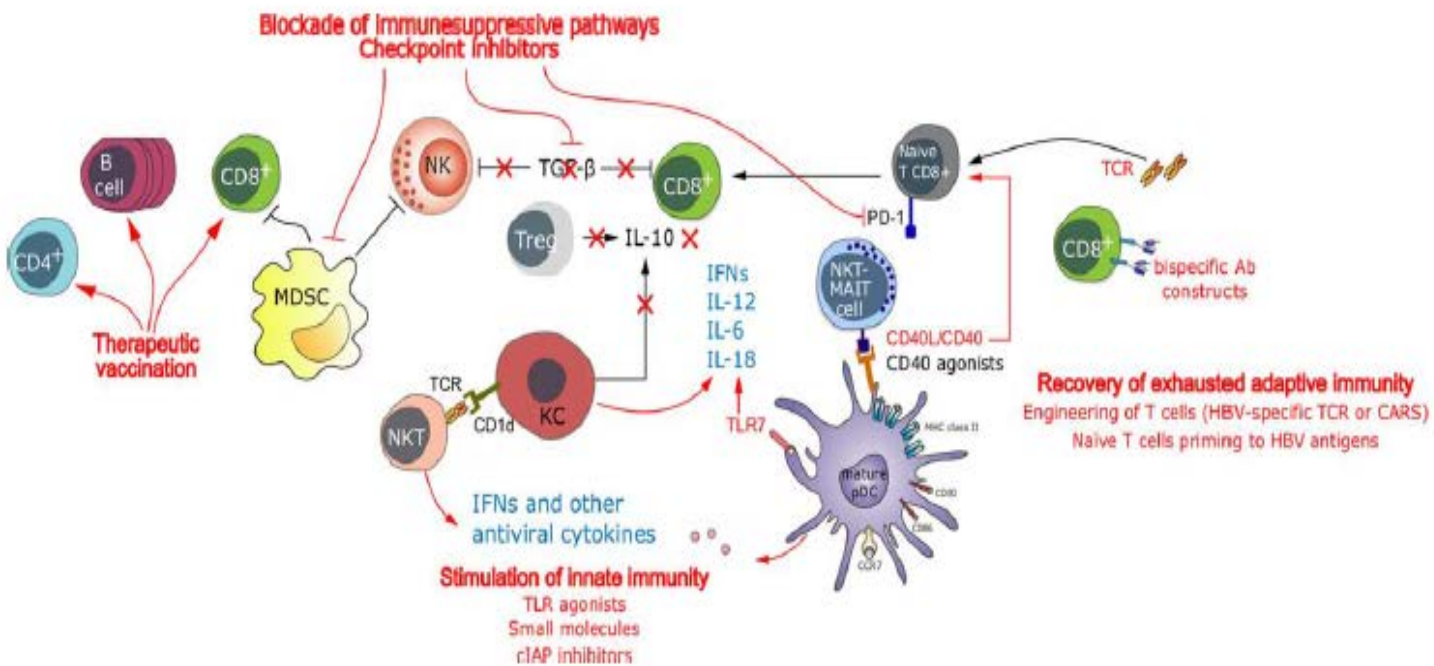
- Prematurely initiating capsid assembly
- Virion production

Targeting HBsAg

- Nucleic acid polymers (NAP)

Lok et al Hepatology 2017;doi 10.1002/hep.29323

Approaches to HBV Cure



Toll-like receptor agonist 7,8 and 9:

- GS-9620

Checkpoint inhibitors

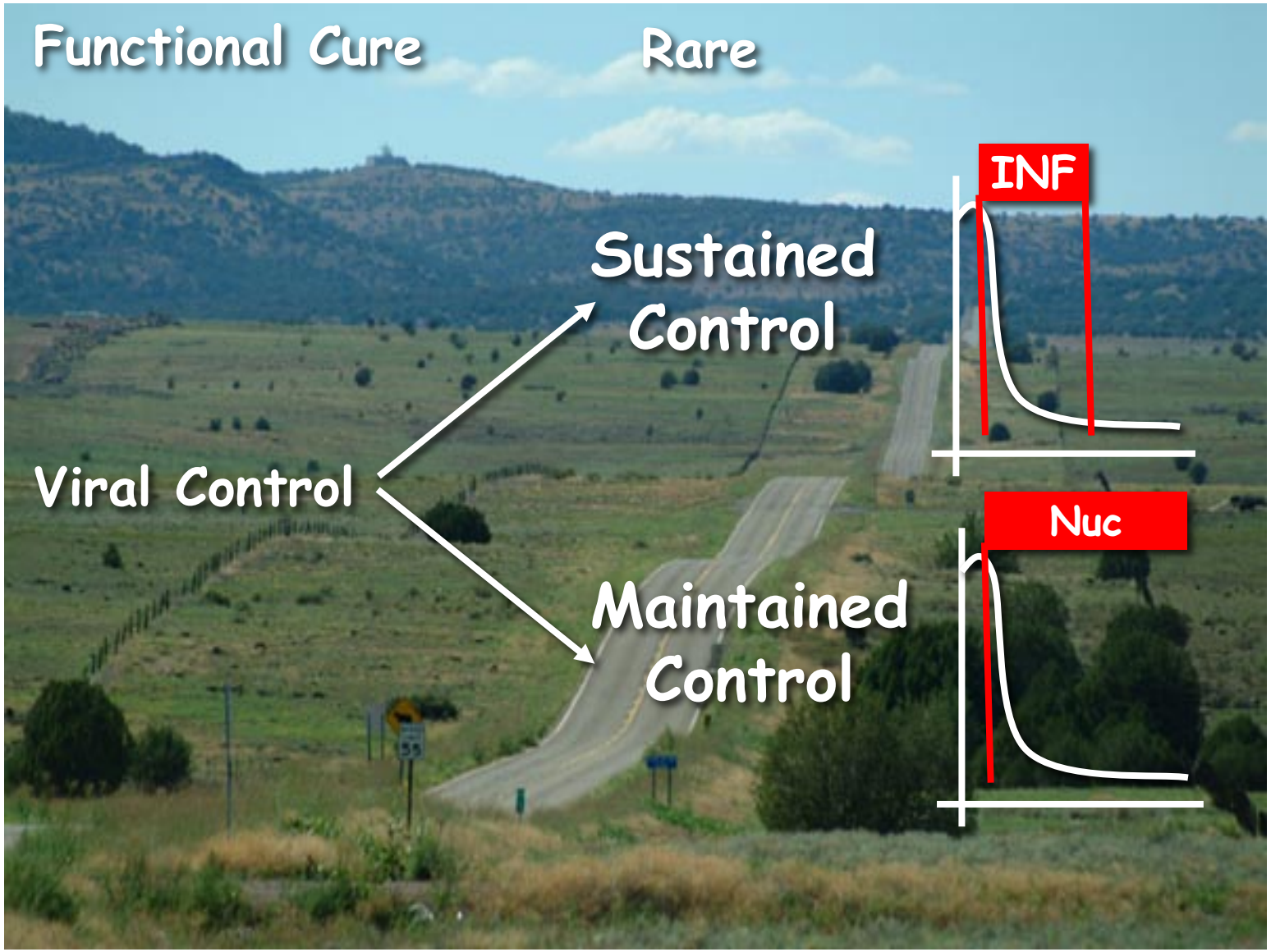
- Nivolumab

Therapeutic vaccination

- HBsAg vaccines
- T-cell vaccine
- DNA vaccination

Genetically engineered T cells

Lok et al Hepatology 2017;doi 10.1002/hep.29323


Functional Cure
Rare
Sustained Control
Viral Control
Maintained Control
INF
Nuc