Hepatitis B: ¿una enfermedad bajo control?

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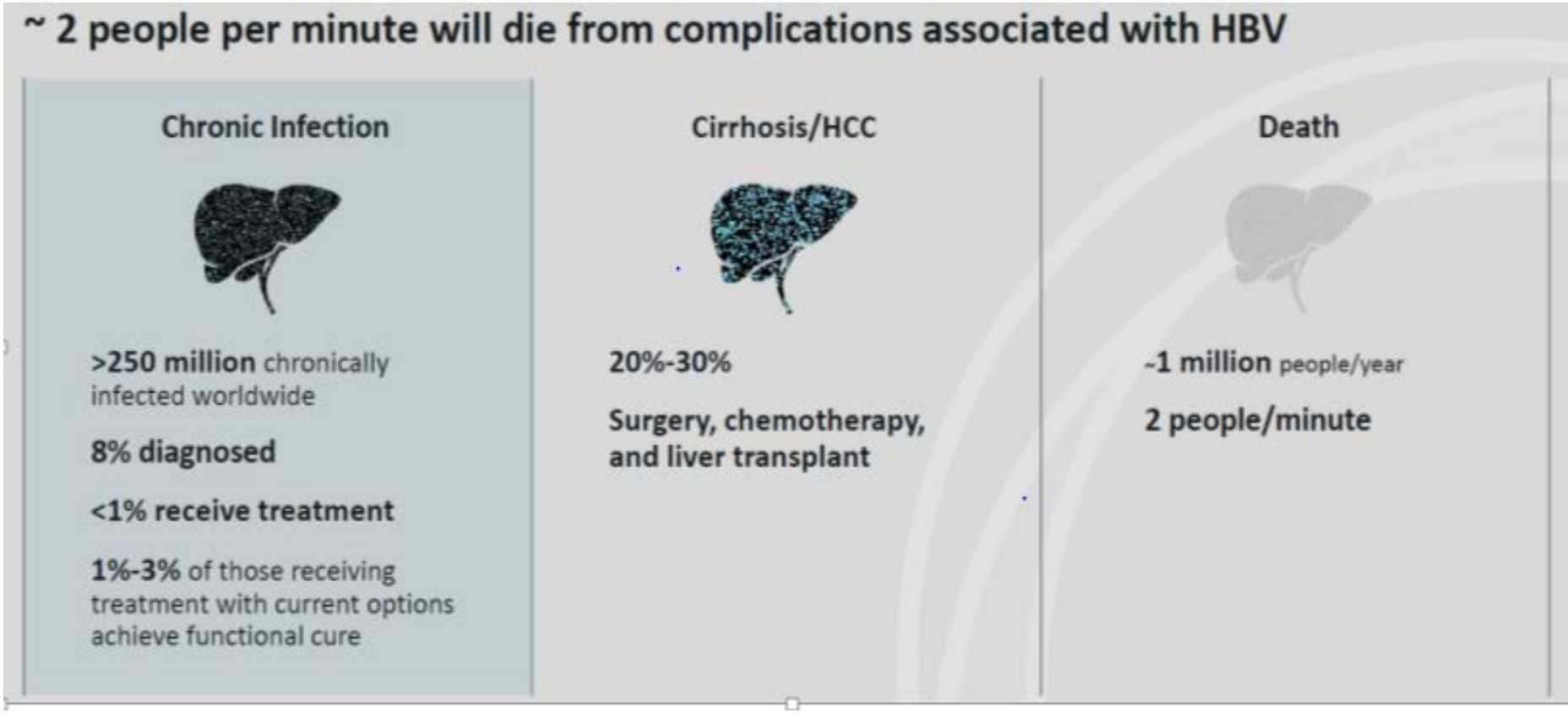
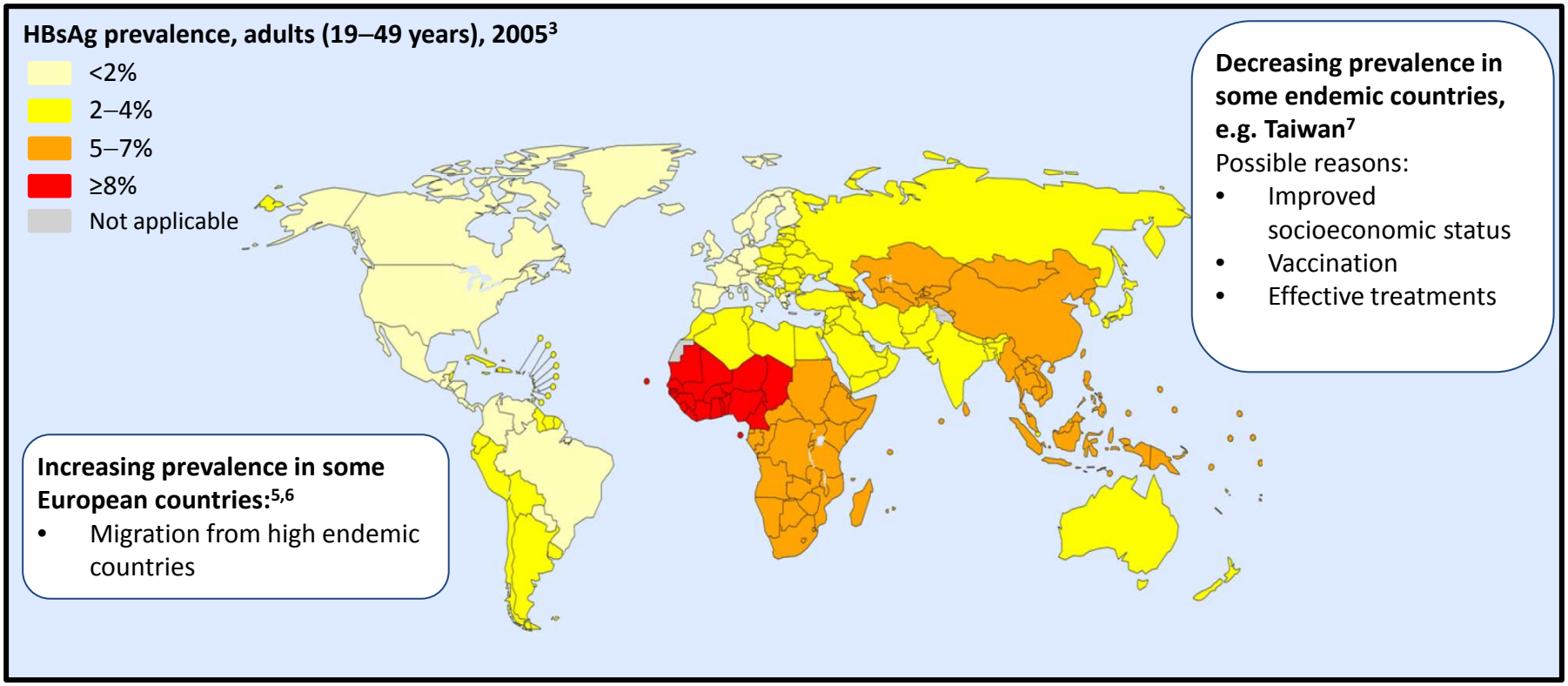
Hepatitis B. Impacto en Salud



Primera causa de cáncer hepático a nivel mundial

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]



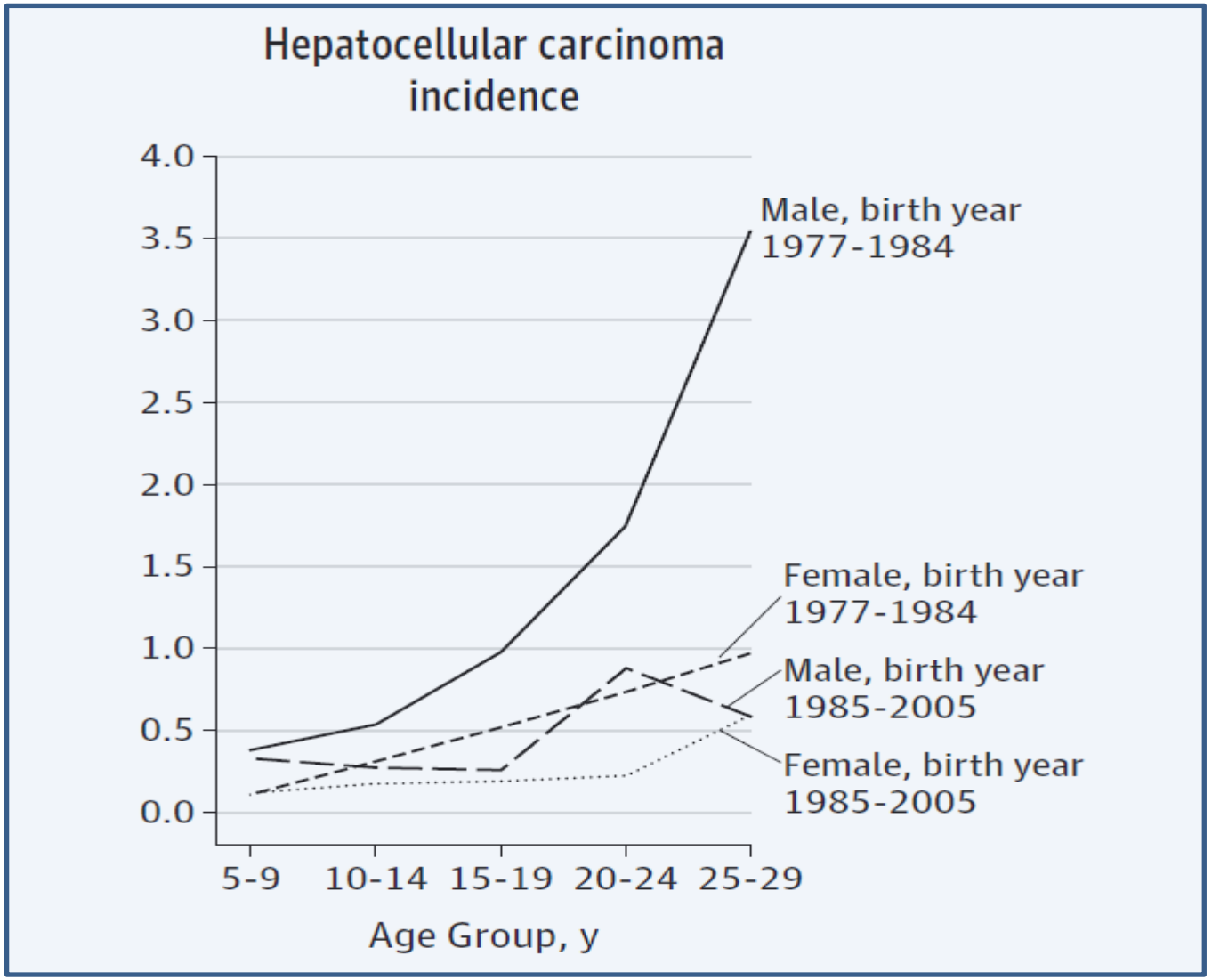
1. EASL CPG HBV. J Hepatol 2017;67:370–98; 2. Schweitzer A, et al. Lancet 2015;386:1546–55;
3. Ott JJ, et al. Vaccine 2012;30:2212–9; 4. GBD 2013 Mortality and Causes of Death Collaborators. Lancet 2015;385:117–71;
5. Coppola N, et al. Euro Surveill 2015;20:30009; 6. Hampel A, et al. Bundesgesundheitsblatt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

Hepatitis B: ¿una enfermedad bajo control?

- Prevenir para evitar nuevas infecciones
  - Vacuna antihepatitis B

- Tratar de los individuos con hepatitis B

Treinta años de seguimiento del Programa Nacional de Vacunación frente a la Hepatitis B en Taiwan



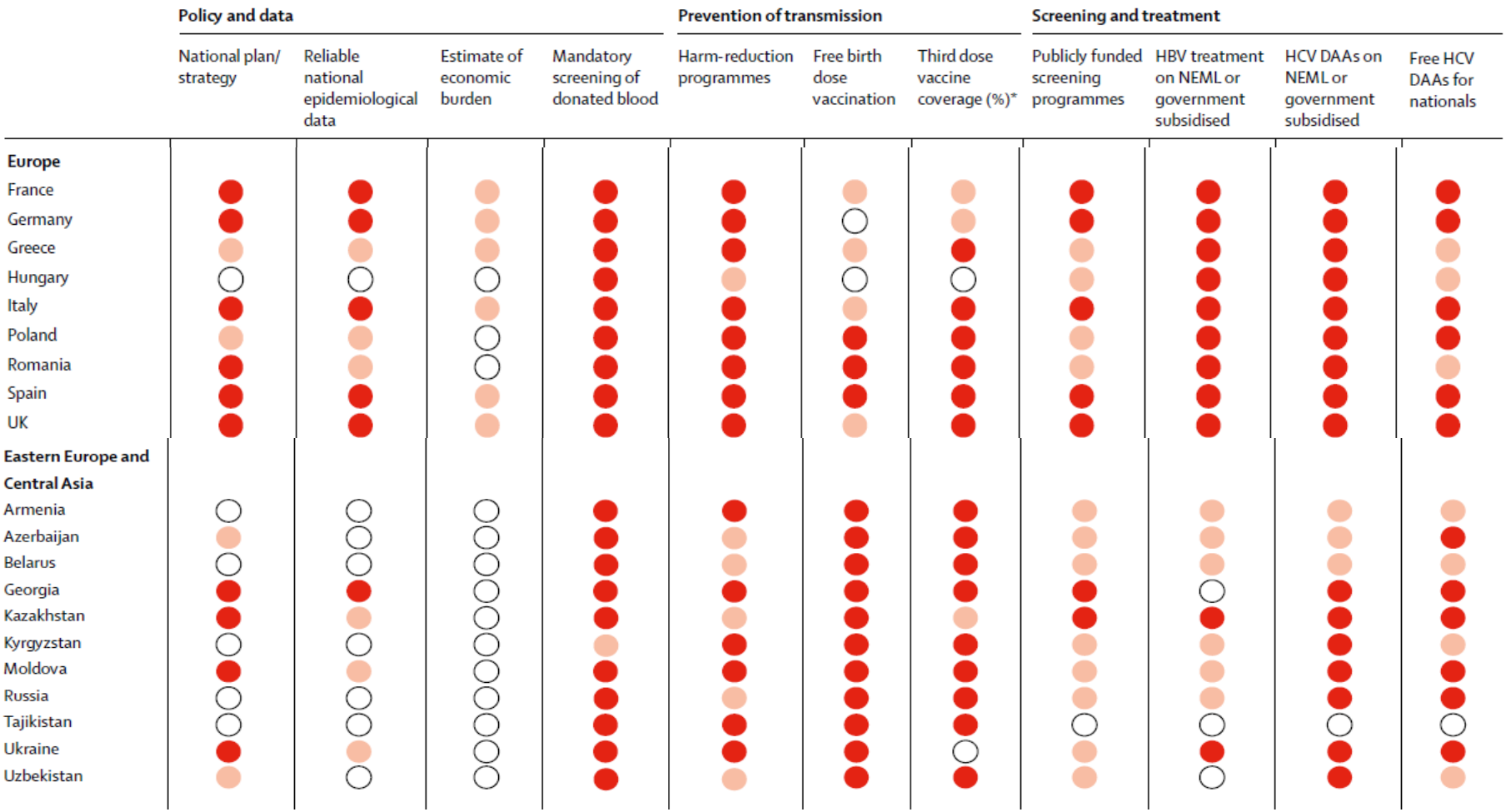
Chiang CJ, et al. JAMA 2013

Baseline estimates (2015) of progress towards elimination targets

	WHO region						World	2020 target	2030 target
	African	Americas	E Med	Euro	SEA	W Pacific			
Population (million)	1000	989	654	914	1945	1867	7369		
Prevalence chronic HBV (%)	6·1%	0·7%	3·3%	1·6%	2%	6·2%	3·5%		
Prevalence chronic HCV (%)	1%	0·7%	2·3%	1·5%	0·5%	0·7%	1%		
Indicators									
Timely birth dose vaccine (%)	10%	72%	23%	39%	34%	84%	39%	50%	90%
Third dose HBV vaccine (%)	76%	89%	80%	81%	87%	90%	84%	90%	90%
Blood donations screened (%)	80%	98%	81%	99·9%	85%	98%	97%	95%	100%
Incidence estimates									
Cumulative incidence of HBV in under 5s (%)	3%	0·2%	1·6%	0·4%	0·7%	0·9%	1·3%	↓30%	↓90%

Cooke GS et al. Lancet Gastroenterol Hepatol. 2019 Feb;4(2):135-184

Policies and Interventions Aimed at Reducing Viral Hepatitis B and C



Red circles denote the existence of a policy; pink circles denote that a policy is in development, is not well applied, or is in place for specific subpopulations; white denotes the absence of a policy. *Shows coverage of infant immunisation programmes including at least three doses of HBV vaccine, where: red symbolises ≥90% coverage (2020 target), pink symbolises 60–90% coverage, and white symbolises <60% coverage or no policy. NEML=national essential medicines list. DAA=direct-acting antiviral.

Cooke GS et al. Lancet Gastroenterol Hepatol. 2019 Feb;4(2):135-184

Charlemagne

The campaign against vaccination

Disease will be a major political battleground in the coming decades

Print edition | Europe ›
Jan 19th 2019

Hepatitis B: ¿una enfermedad bajo control?

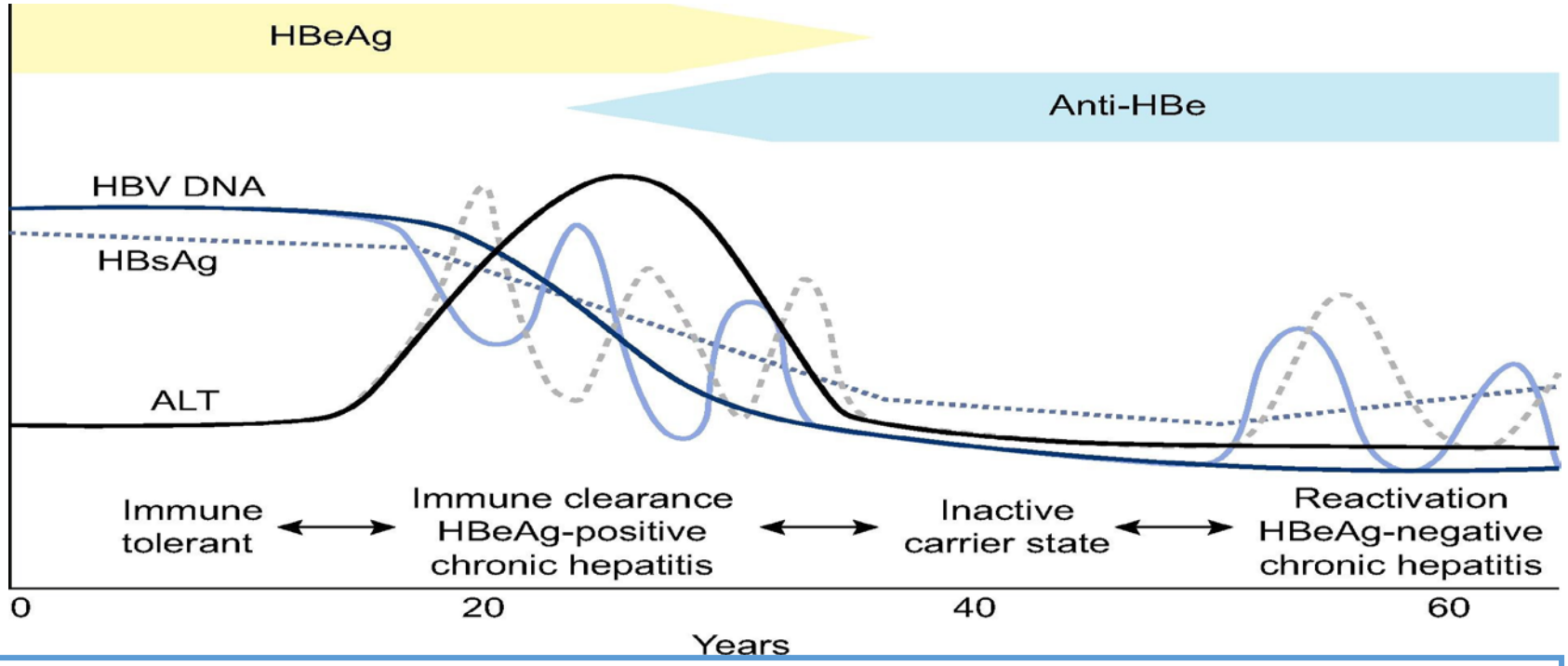
- Prevenir para evitar nuevas infecciones
  - Vacuna antihepatitis B

- Tratar de los individuos con hepatitis B
  - Control de la infección
  - No curable en la mayoría de los casos

Hepatitis B una enfermedad tratable pero no curable

- Identificar a los candidatos al tratamiento

Phases of chronic HBV infection



New no-menclature	HBeAg-positive chronic HBV infection	HBeAg-positive chronic hepatitis B	HBeAg-negative chronic HBV infection	HBeAg-negative chronic hepatitis B

EASL HBV CPGs 2017. J Hepatol 2017; 67: 370-398.

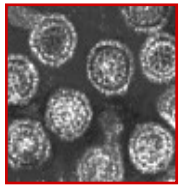
Current treatment strategies for chronic hepatitis B: main concepts and features

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 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

Current treatments: virus suppression and sustained disease control



NUCs
Virus suppression

Normal liver

Chronic Hepatitis

HBsAg loss rate
Max 10% after 5 years

Cirrhosis

HCC

Decreased inflammation/fibrosis
Decreased progression

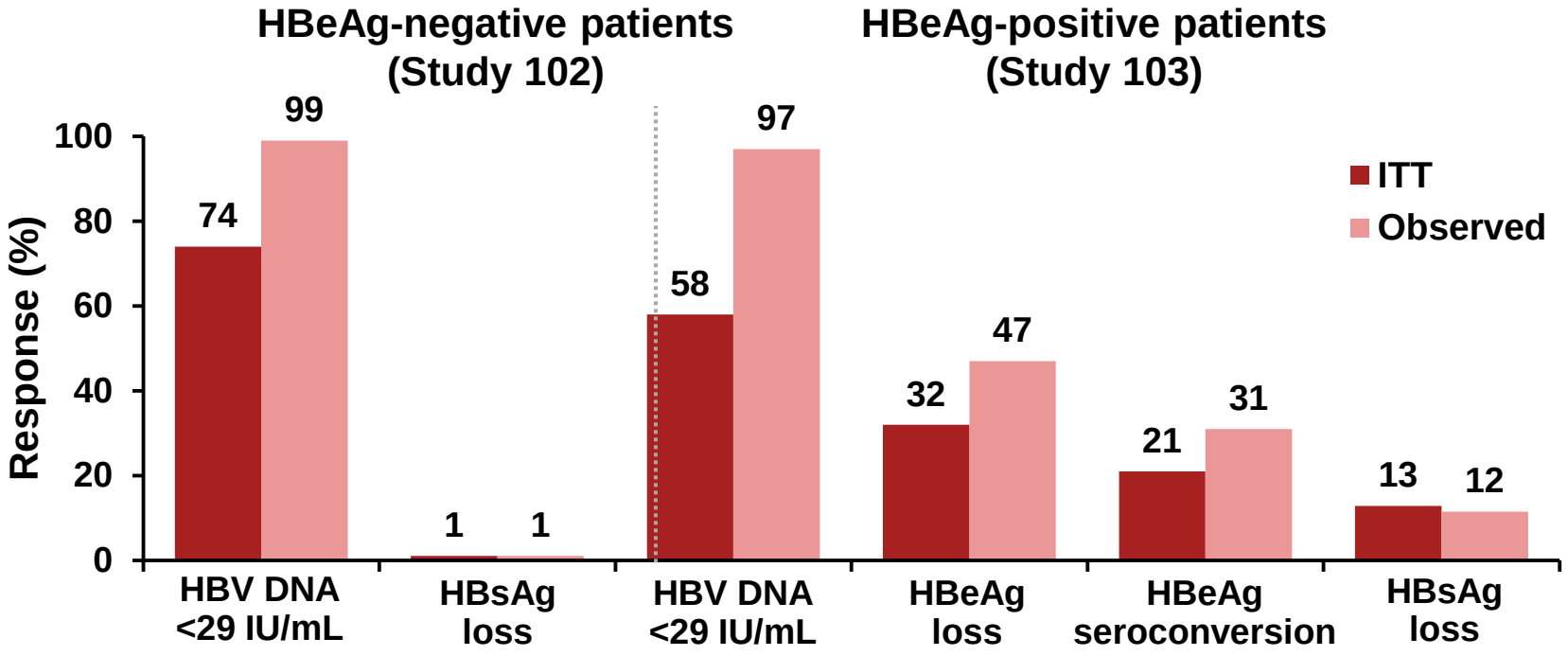
Reversal of fibrosis
Decreased progression

Decreased incidence
but not eliminated

Liaw YF et al, N Engl J Med. 2004; Chang et al, Hepatology 2010; Marcellin et al, Lancet 2013; Hosaka et al, Hepatology 2013; Kim et al, Cancer 2015; Papatheodoridis et al, J Hepatol 2015

Long-term Therapy (8 years) with TDF Is Effective in CHB Patients (Studies 102/103)

- 8-year follow-up of TDF in two randomised, double-blind studies in primarily treatment-naïve CHB patients

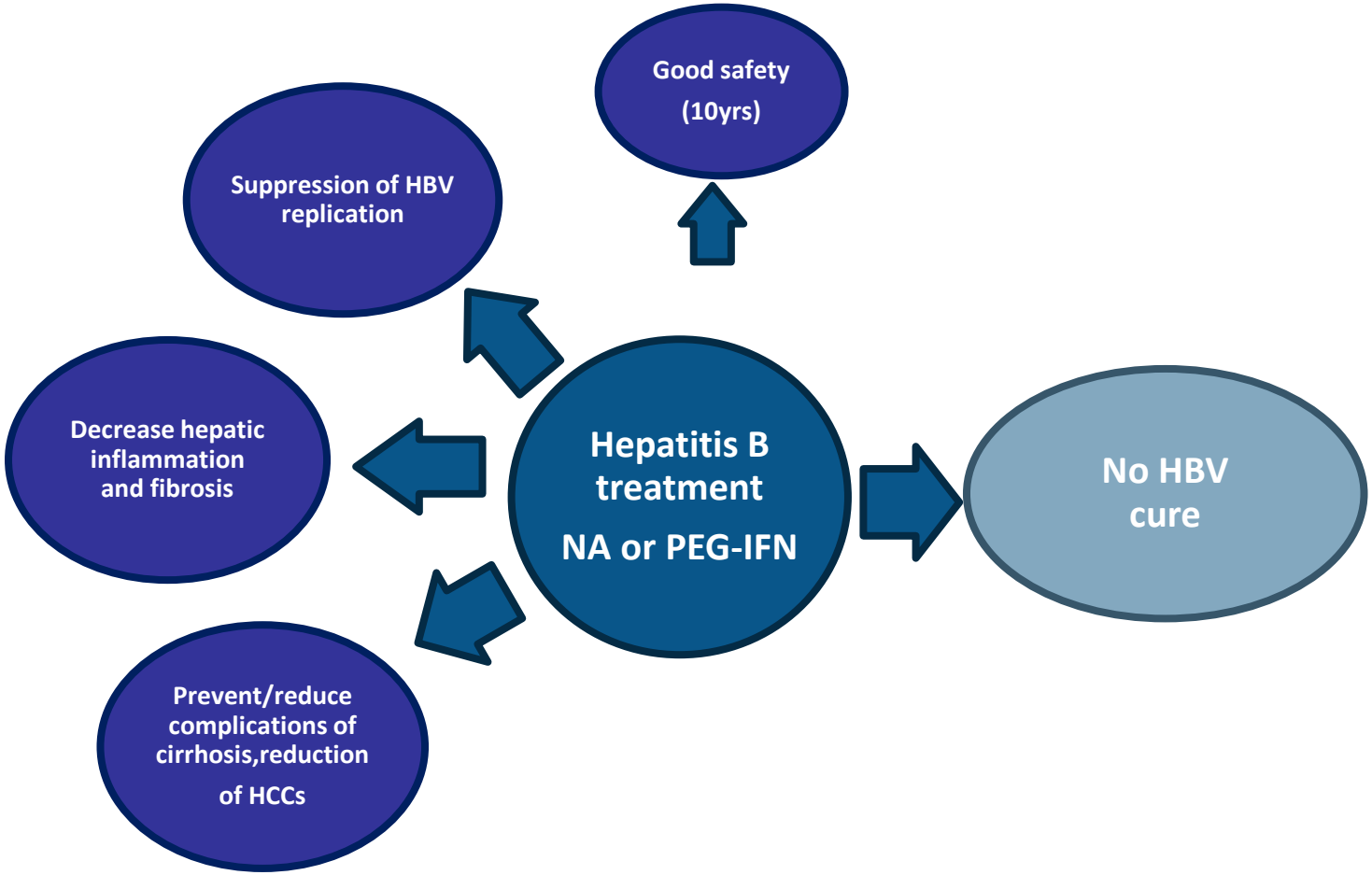


No resistance in HBeAg-negative or HBeAg-positive patients up to Year 8

TDF: tenofovir disoproxil fumarate; HBeAg: hepatitis B 'e' antigen; HBsAg: hepatitis B surface antigen; ITT: intention-to-treat

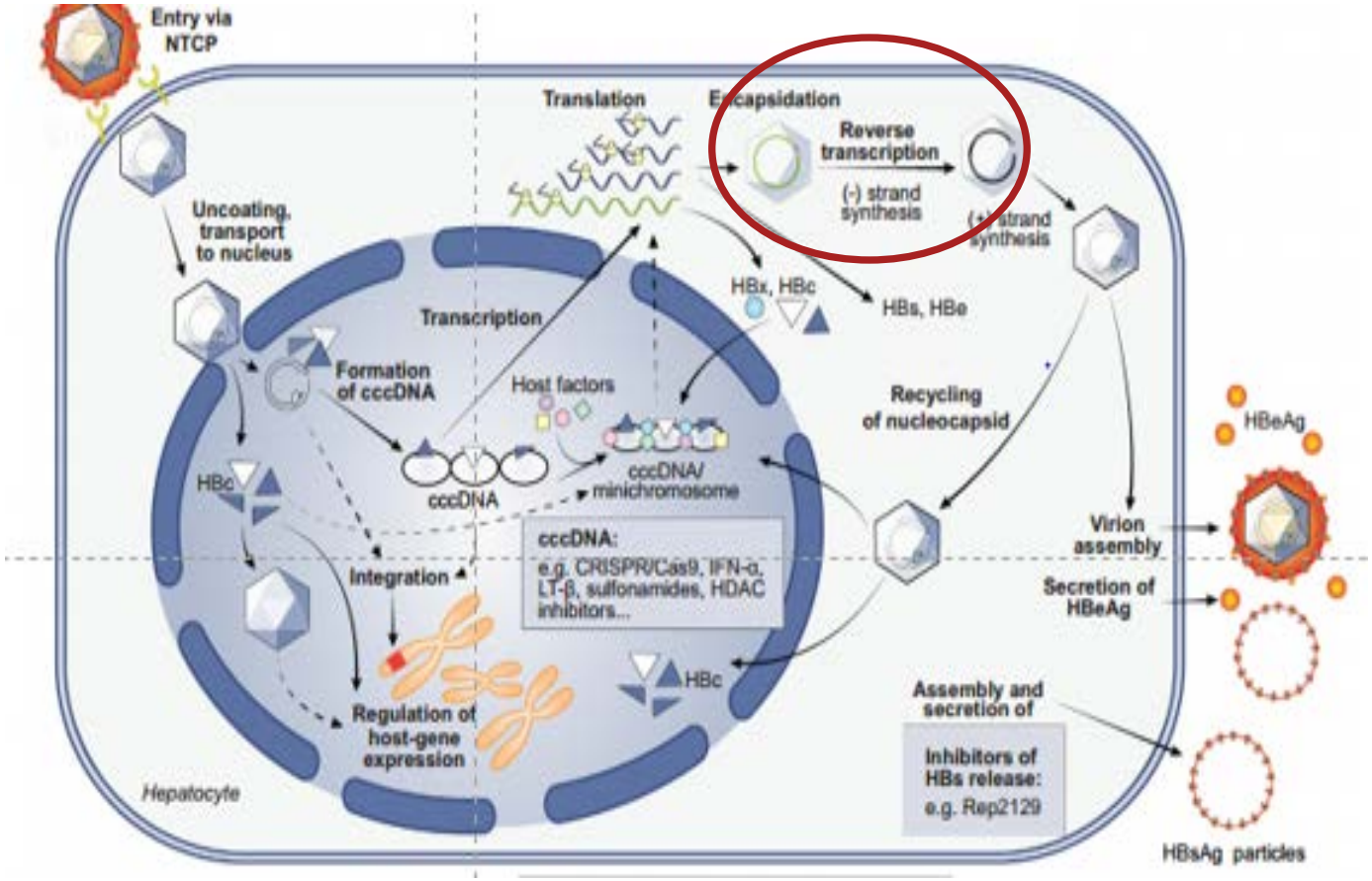
Marcellin P, et al. AASLD 2014; Oral #229

Achievements and ongoing challenges Hepatitis B



Liaw YF, et al. N Engl J Med 2004;351:1521–31;
Marcellin P, et al. Lancet 2013;381:468–75
Dandri M, Petersen J. Clin Infect Dis 2016;62:281-8

NAs Target Reverse Transcription



NA: nucleot(s)ide analogue

Durantel D et al. J Hepatol 2016;64:S117-S131

Current Treatments Do Not Completely Suppress HBV DNA

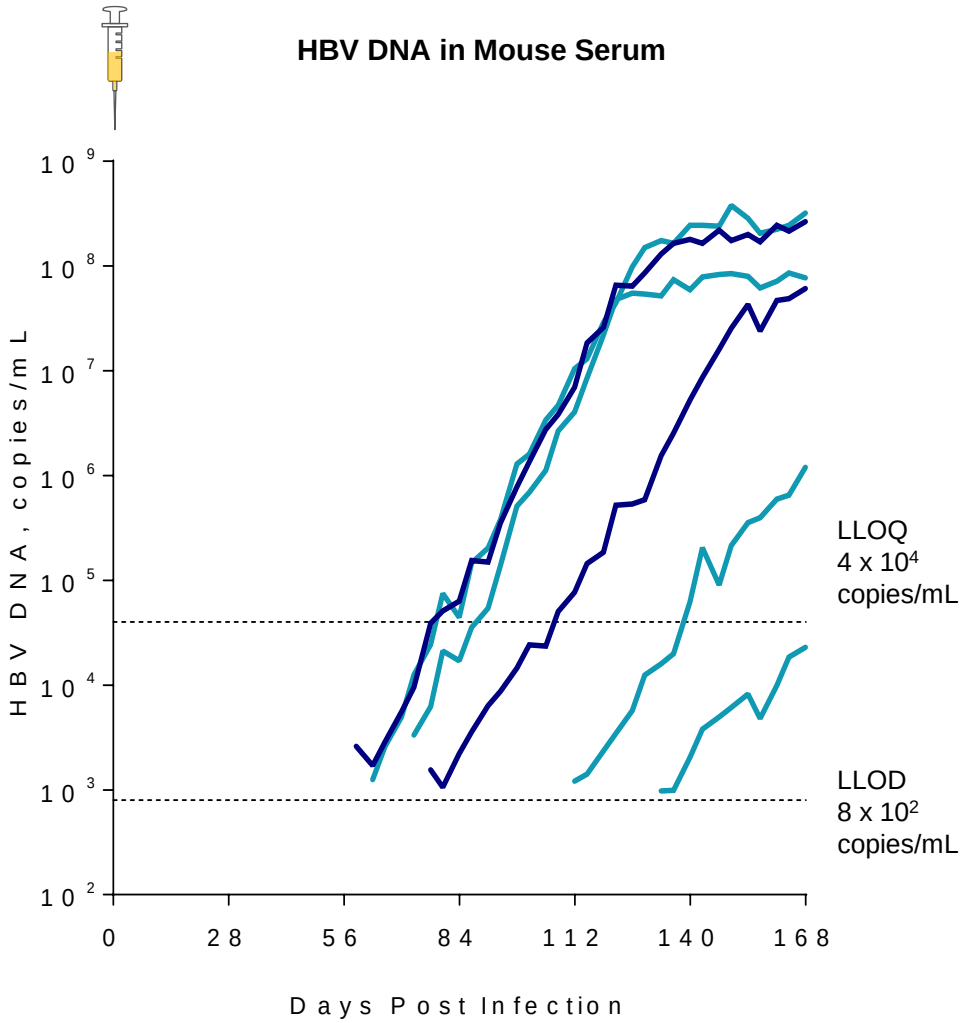
- In the majority of patients, treatment with TDF or ETV results in
  - HBV DNA suppression to <LLOQ (29 IU/mL)
  - ALT normalization and fibrosis improvement
- After 240 weeks of TDF HBV DNA remains detectable in the majority of treated patients with viral load <LLOQ
  - HBeAg negative 60%, HBeAg positive 70%
- Ongoing replication despite nucleos(t)ide therapy may provide a mechanism for long-term viral persistence

Marcellin et al. Hepatology 2014;60:1093A.

Evidence for the Presence of Infectious Virus in the Serum from Chronic Hepatitis B Patients Suppressed on Nucleos(t)ide Therapy with Detectable but not Quantifiable HBV DNA

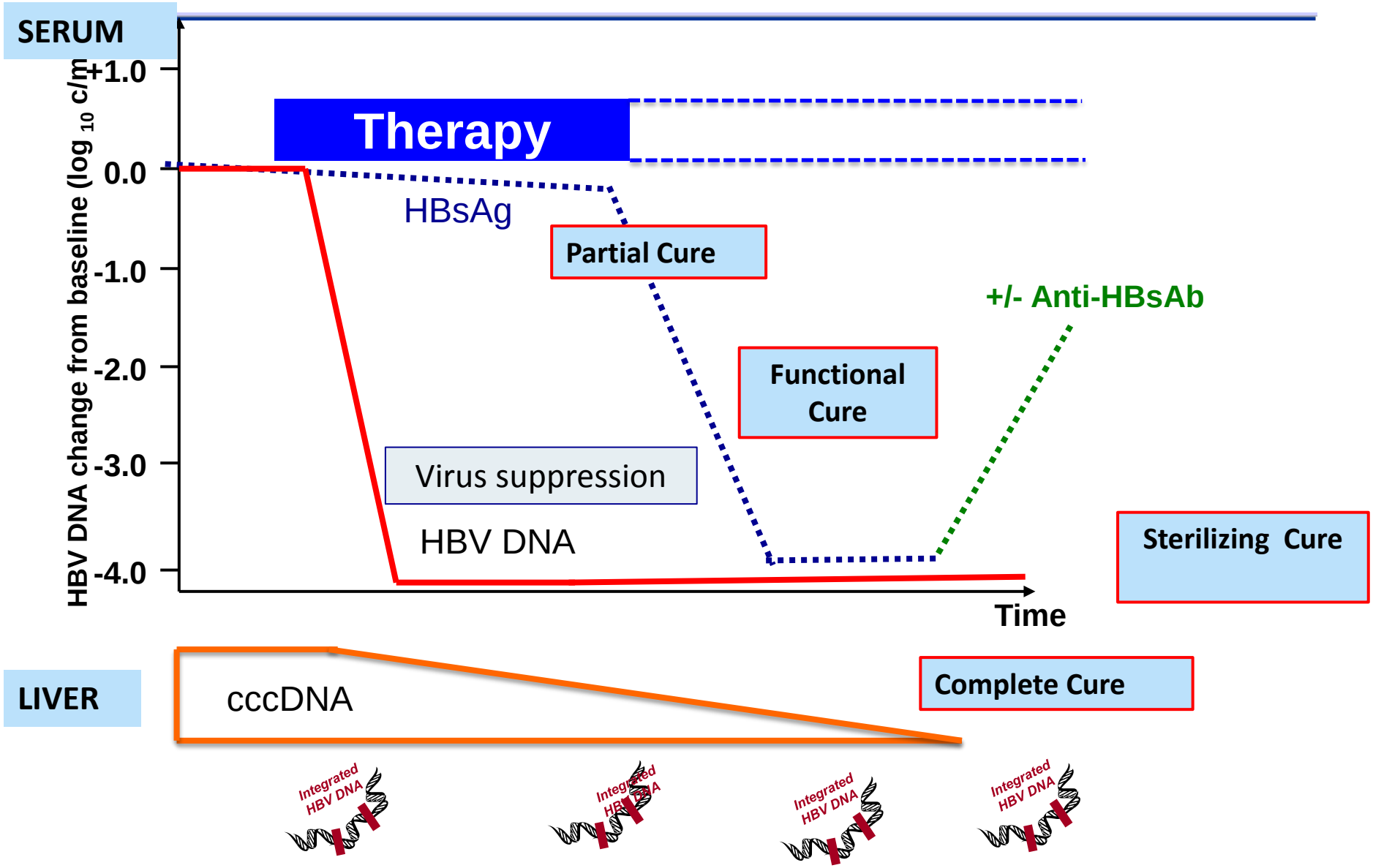
Humanized mice support infection with HBV derived from patient serum

Sera from patients suppressed to <LLOQ (29 IU/mL) on NUC therapy contains infectious HBV



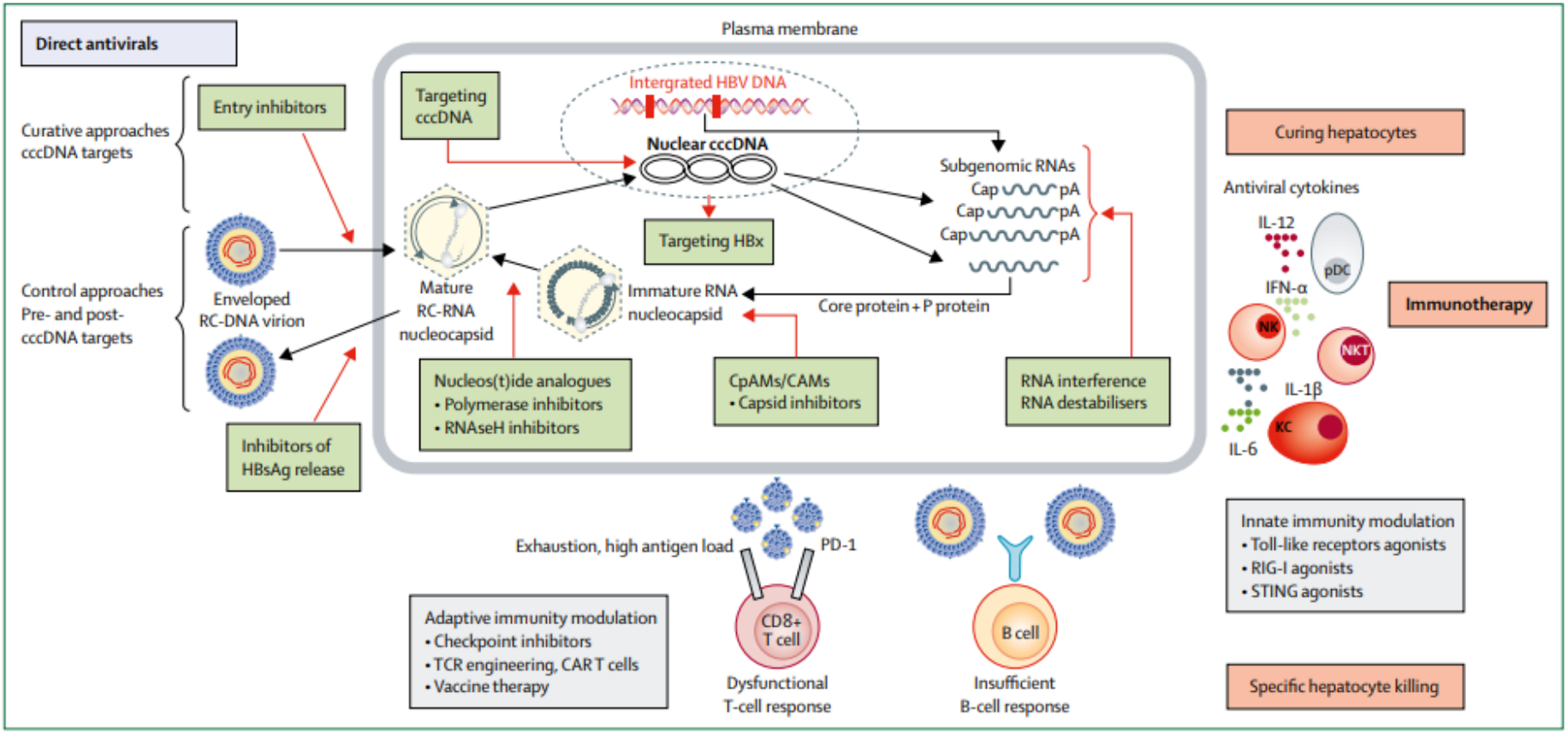
Burdette D et al EASL 2019

Definition of HBV cure: what do we want to achieve ?



Lok et al, Hepatology / J Hepatol joint publication, in press; Testoni et al, Sem Liver Dis, in press.

HBV virological and immunological targets that will be necessary for treatment and cure of chronic hepatitis B

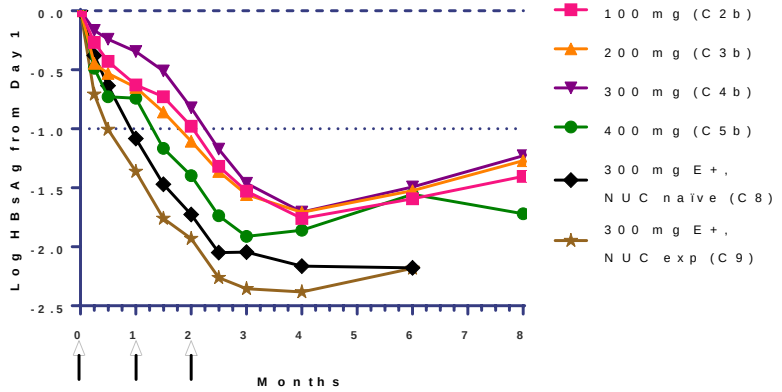


Revill P et al Lancet Gastro Hepatol 2019

Short-term RNA interference therapy in chronic hepatitis B using JNJ-3989 brings majority of patients to HBsAg <100 IU/ml threshold

Patients with chronic HBV received 3 SC doses of JNJ-3989 weekly to monthly together with ETV or TDF

Mean HBsAg reductions from baseline



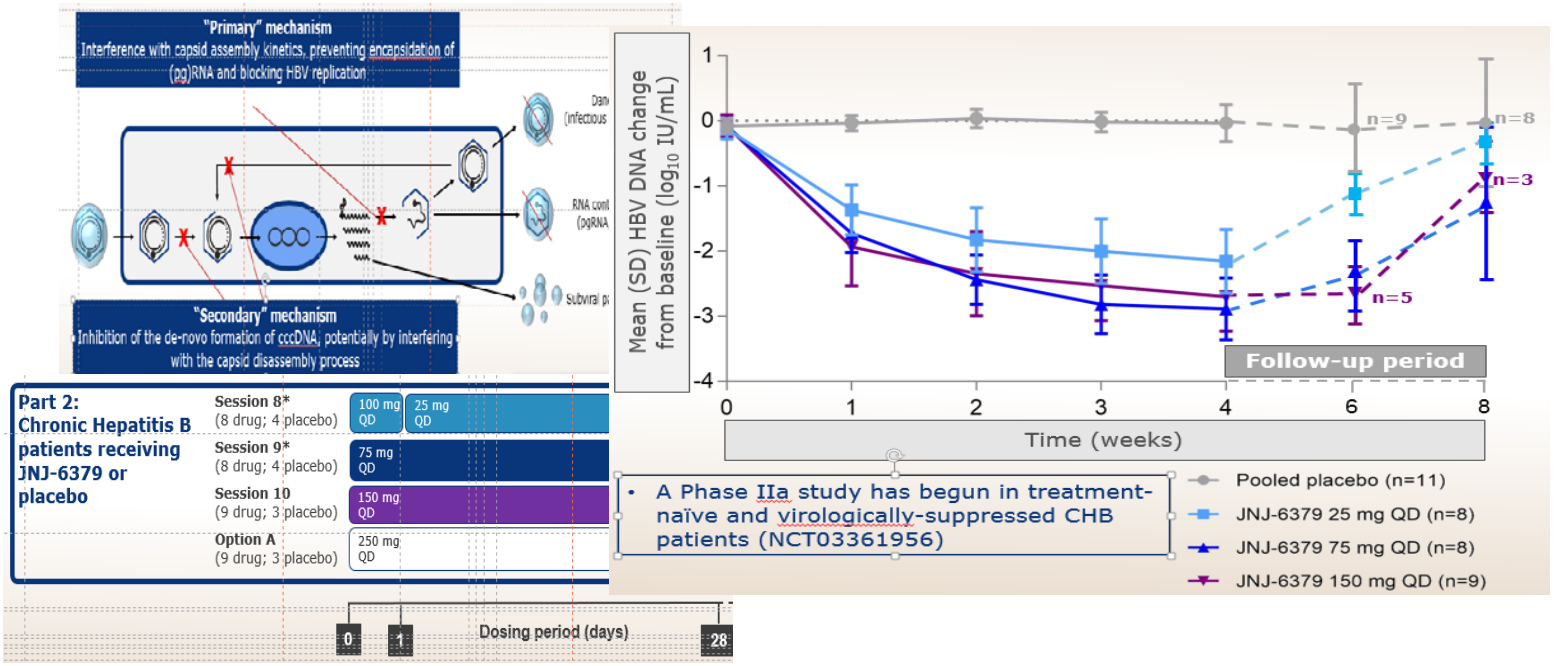
Baseline HBsAg		
Threshold	N	Percent
>100 IU/ml	37 of 40	93%
NADIR HBsAg		
Threshold	N	Percent
≤100 IU/ml	35 of 40	88%
≤10 IU/ml	17 of 40	43%

- HBsAg was reduced as follows:
  - To <100 IU/mL in 88%
  - By ≥1 Log_{10} IU/mL in 100%
  - Both thresholds have been associated with increased probability of HBsAg clearance when stopping NUC treatment[1]

JNJ-3989 exhibits characteristics desirable for a cornerstone therapy in finite regimens aimed at HBsAg seroclearance in patients with chronic hepatitis B infection

Yuen MF, et al. ILC 2019; PS-080

Safety and antiviral activity of novel capsid assembly modulator JNJ-6379 in treatment-naive chronic hepatitis B patients without cirrhosis



Safety profile was good

HBV DNA undetectable: 38% of cases 75 mg and 38% of 150mg
HBV RNA undetectable: 75-80% cases with same doses
No Changes in HBsAg levels

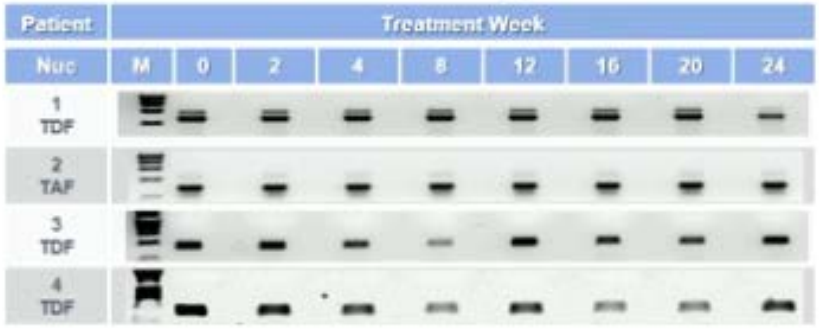
Zoulim F et al. IILC 2018; LBO-004

Interim data from two Phase 2a studies of ABI-H0731 suggest good tolerability and enhanced antiviral efficacy in combination with NAs in chronic hepatitis B infection slide 11

Interim analysis includes 64/73 suppressed individuals that have completed the Week 12 assessment and 9 that have completed week 24 assessments

At Week 24, longitudinal serum samples were assayed for detectable virus

Nuc Monotherapy

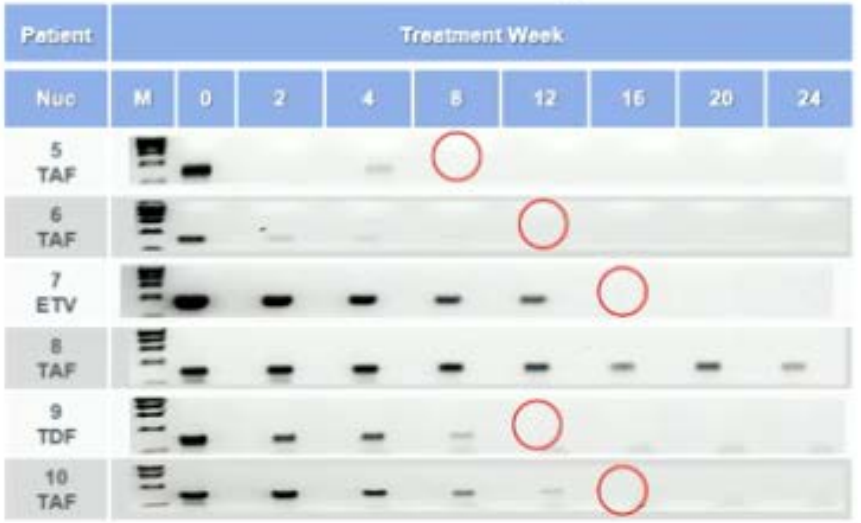


HBV DNA PCR Assay To Quantitate Low Level Viremia

- DNA purified from longitudinal serum samples (0 – 24 Wk)
- PCR amplification (40-45 cycles) using individually optimized primers

Residual viremia not eliminated by Nuc

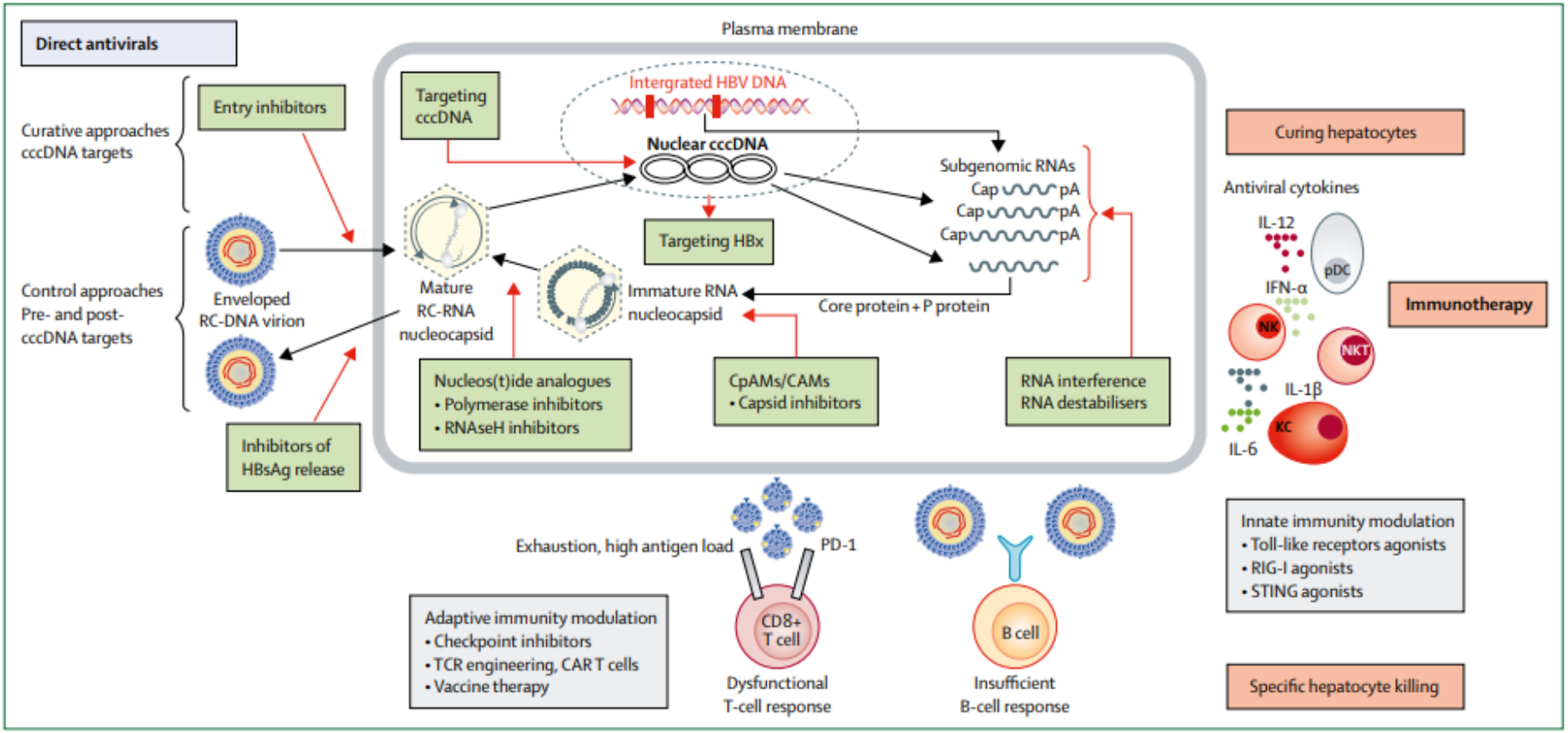
731 Combo Therapy



Residual viremia declines below detection (2-5 IU/mL)

Lalezari J et al. EASL 2019

HBV virological and immunological targets that will be necessary for treatment and cure of chronic hepatitis



Revill P et al Lancet Gastro Hepatol 2019

Resumen

Hepatitis B es una enfermedad frecuente de dinámica de presentación heterogénea . Existe diferentes fases en su historia natural

Vacuna de la hepatitis B previene la infección por VHB, disminuye el riesgo de cáncer hepatico pero su implementación varia en distintos países

Los flujos migratorios ayudan a la diseminación de esta enfermedad

El tratamiento antiviral previene el desarrollo de cirrosis y sus complicaciones y reduce el riego de desarrollar cáncer hepático

La curación de la infección definida por la perdida del HBsAg es muy baja con los tratamiento disponibles lo que hace necesario nuevas estrategias terapéuticas

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