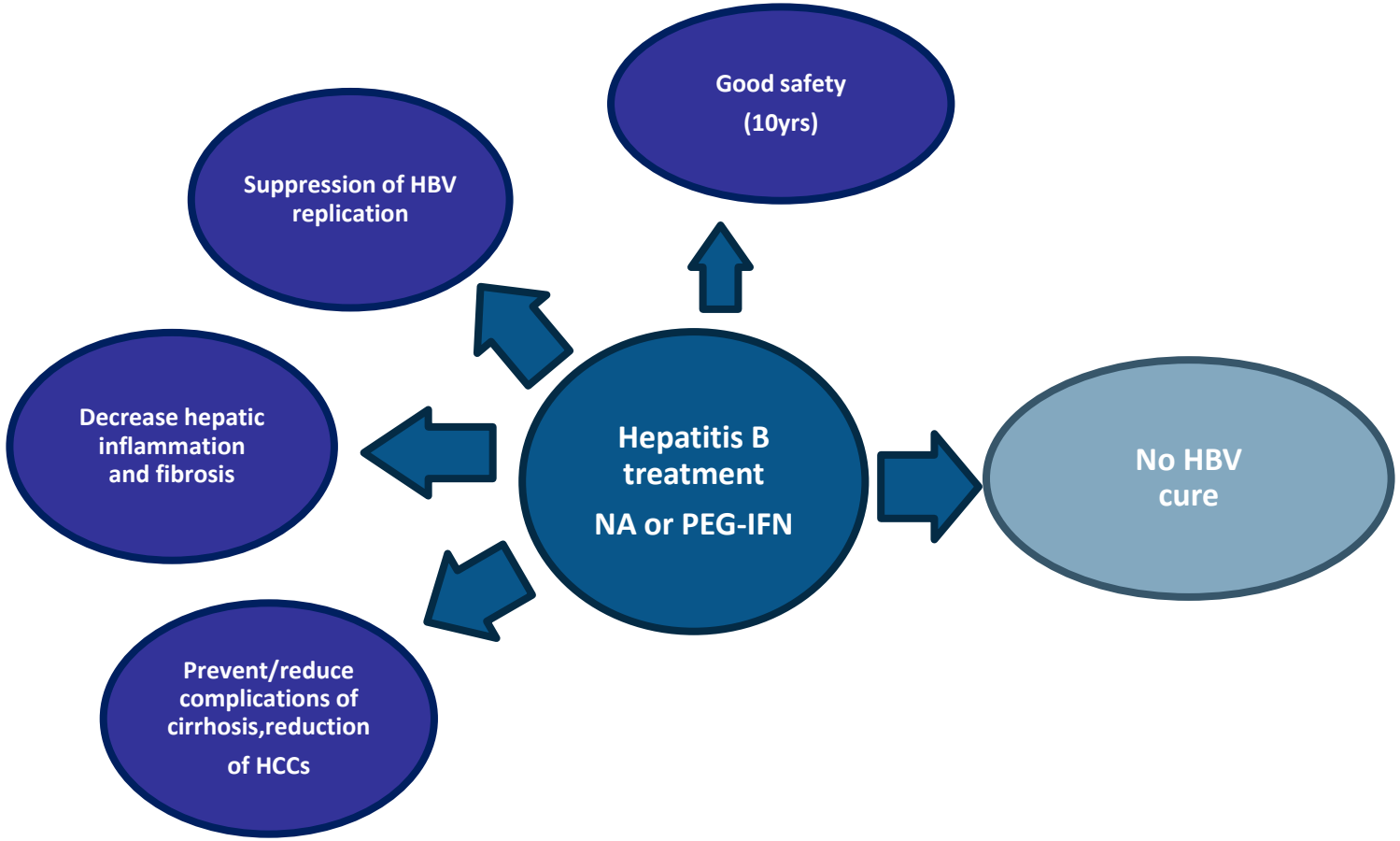
La curación de la hepatitis B y D un sueño inalcanzable.

Dr. Rafael Esteban

Hospital Universitari Vall d'Hebron.

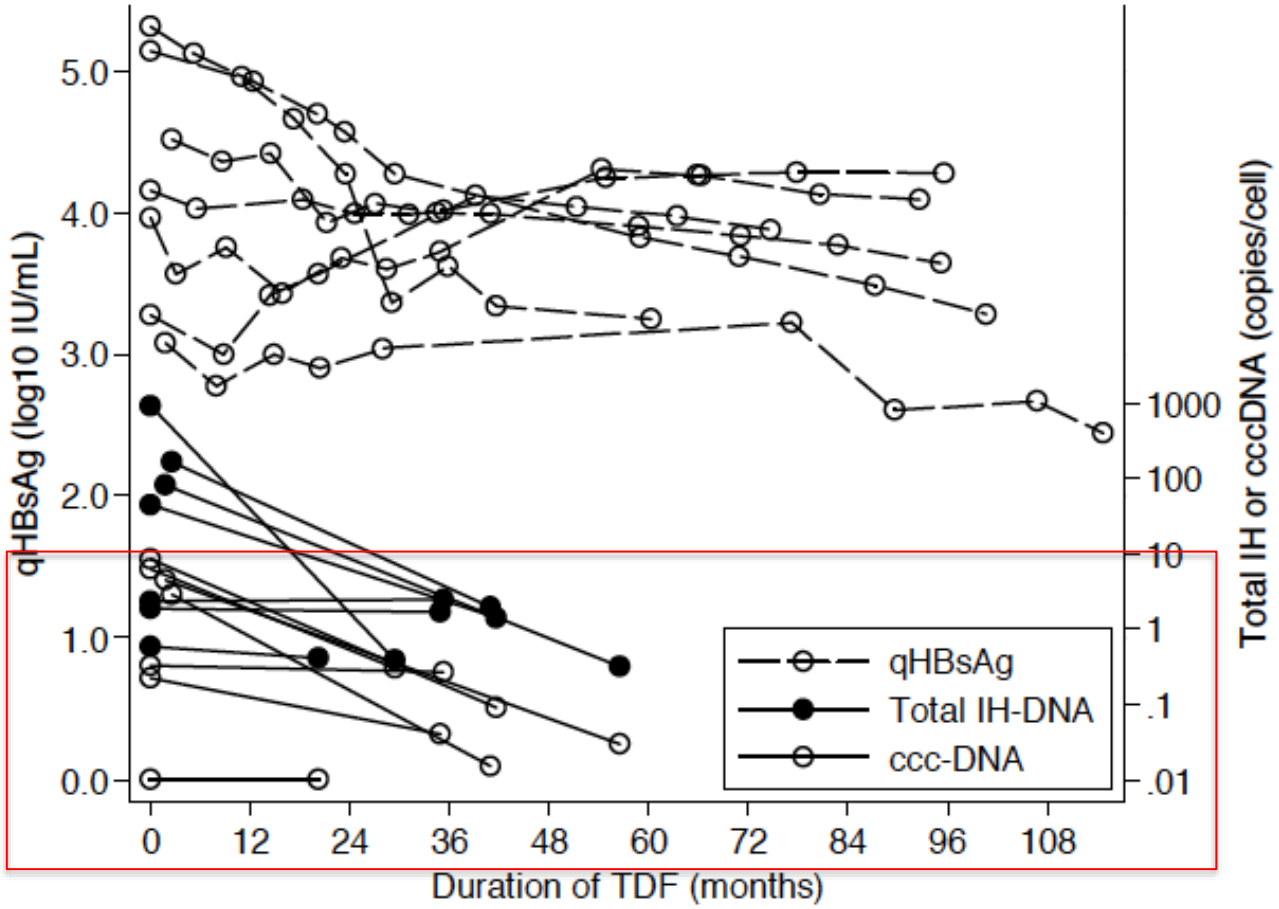
Barcelona

Achievements of the current strategies for therapy of Chronic 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

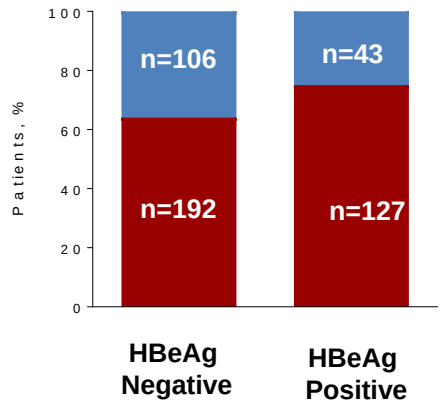
Persistence of intrahepatic viral DNA synthesis during long Tenofovir therapy (HIV-HBV cohort)

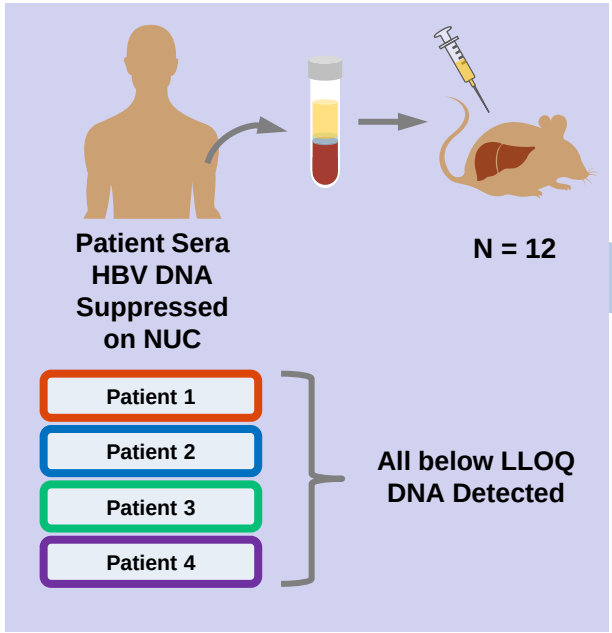


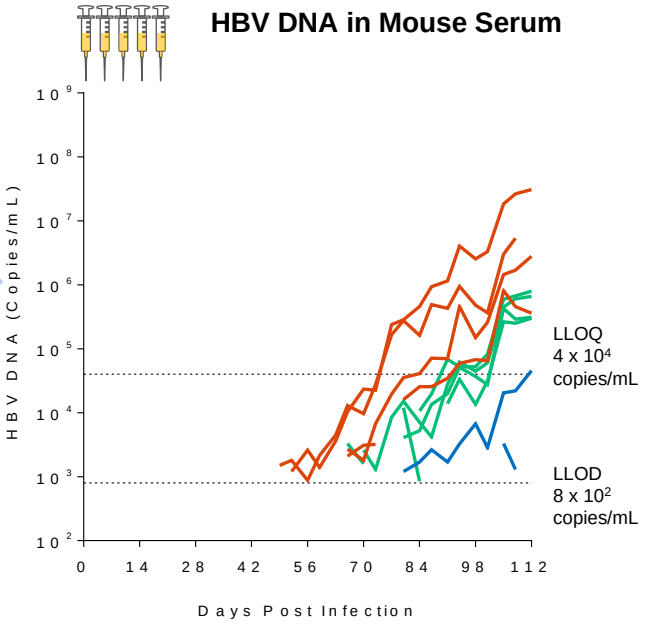
New round of infection and/or replenishment of the cccDNA pool occur despite « viral suppression »

Boyd et al, J Hepatol 2016

Patient Sera with HBV DNA Below LLOQ Under TDF Is Infectious



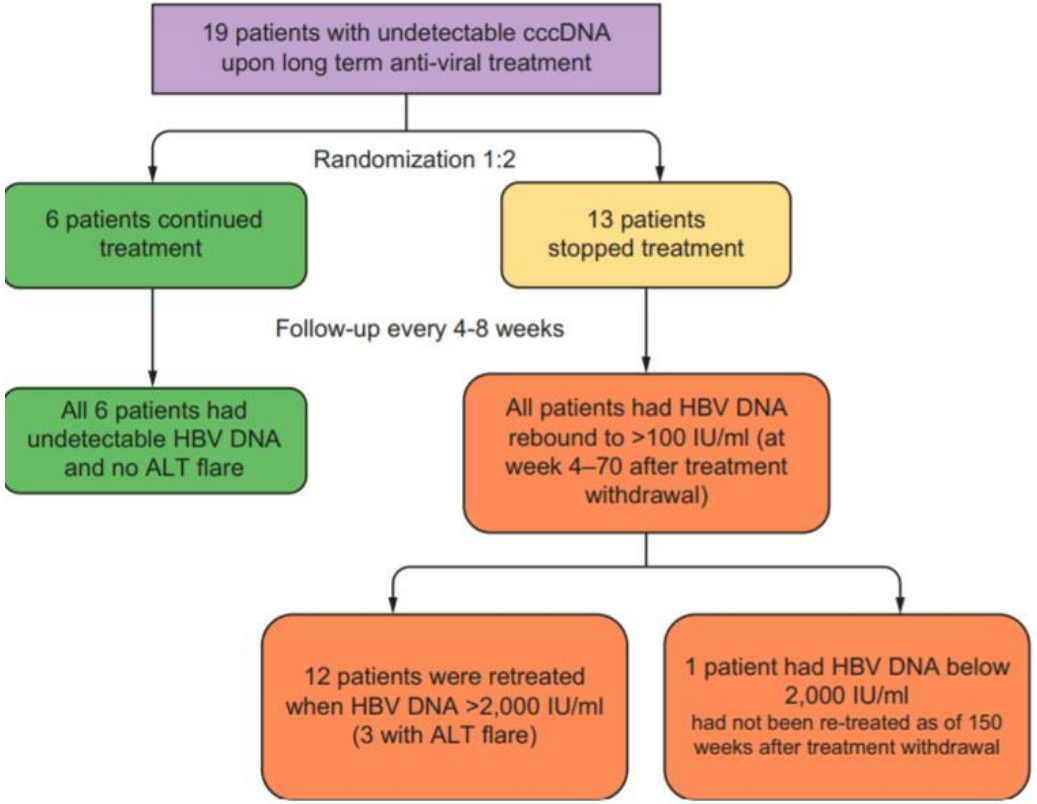


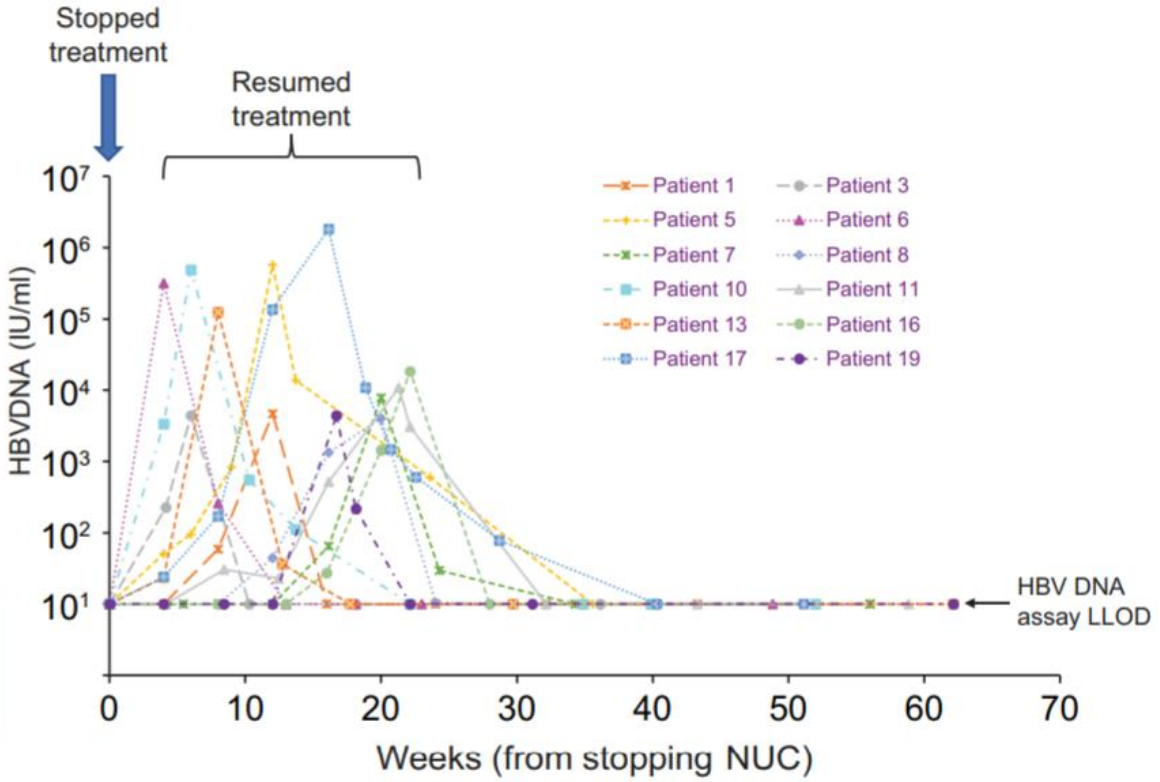


Marcellin et al.
Hepatology 2014;60:1093A.

Burdette et al, EASL ILC 2019

Rebound of HBV DNA after cessation of NU in chronic hepatitis B patients with undetectable cccDNA

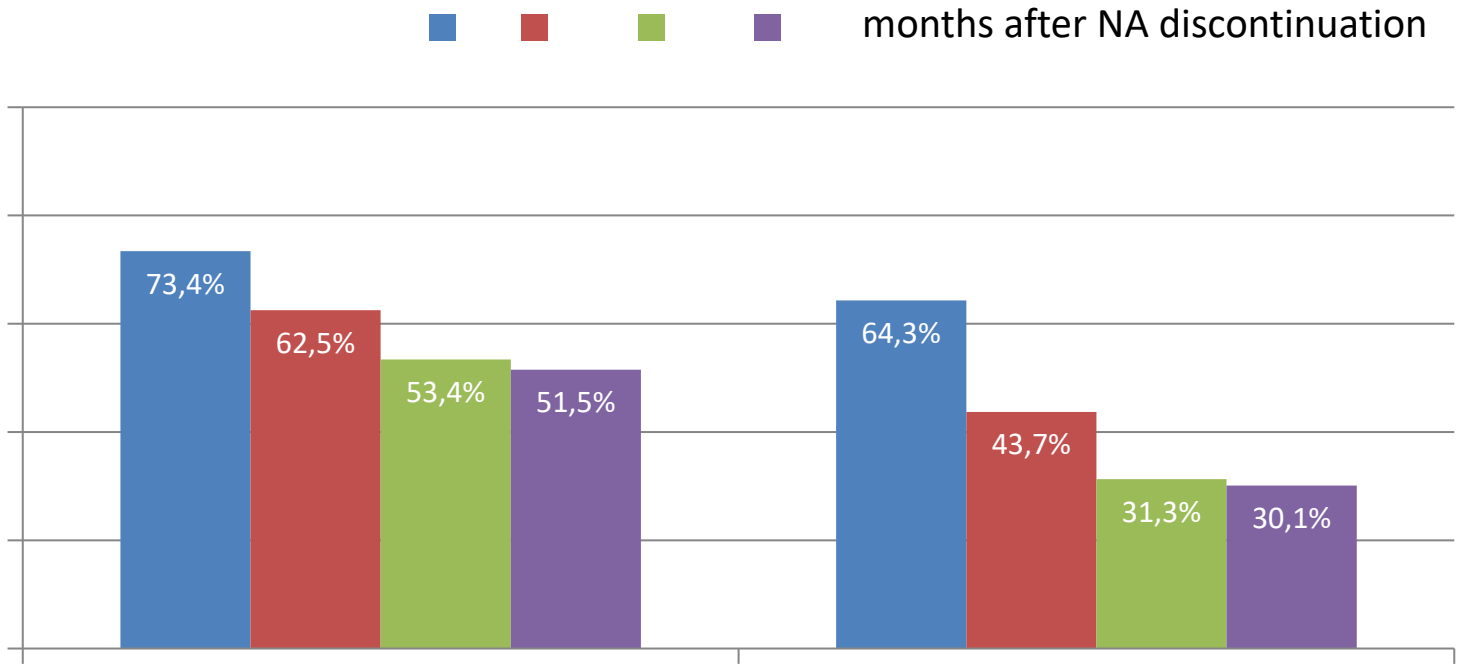




Lai C-L et al. J Hep REP 2020

Significant proportion of patients have relapse after discontinuation of NA

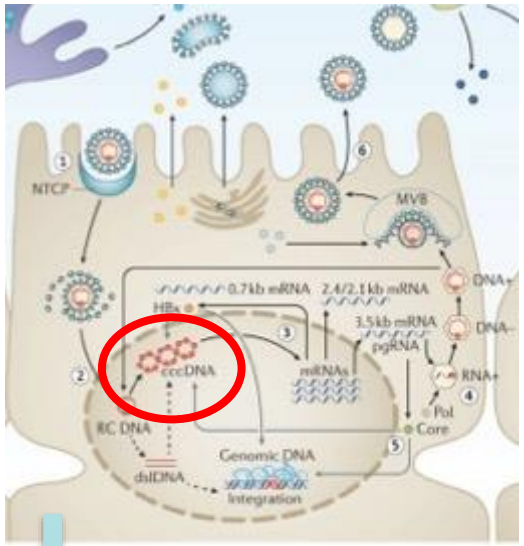
- Pooled analysis of 25 studies among patients stopped NA
- HBeAg seroconversion in HBeAg positive and HBV DNA undetectable in HBeAg negative pts on NA



Post-treastment Virologic response = HBV DNA <20,000 IU/ml

Papatheodoridis G, et al. Hepatology 2016;63:1481-92

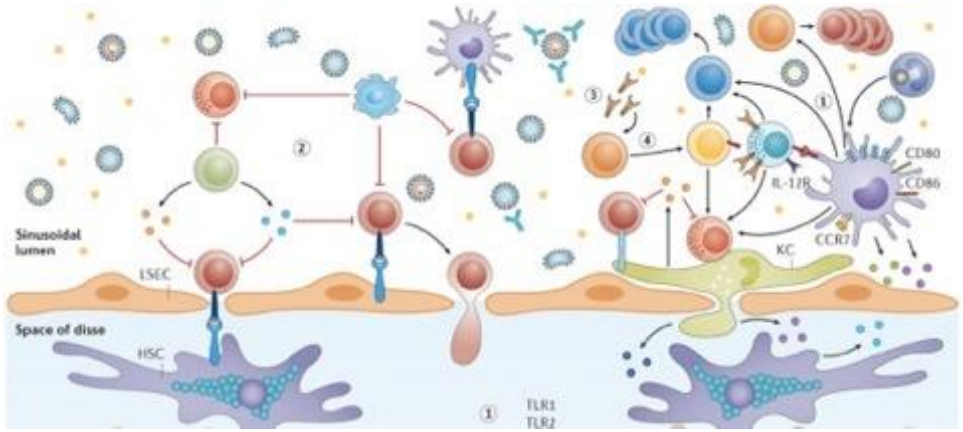
Barriers to eradicating HBV



cccDNA reservoir
Long t1/2
Continuous replenishment
Not affected by NAs and IFN

Integrated forms

HBV persistence



Defective CD8+ responses

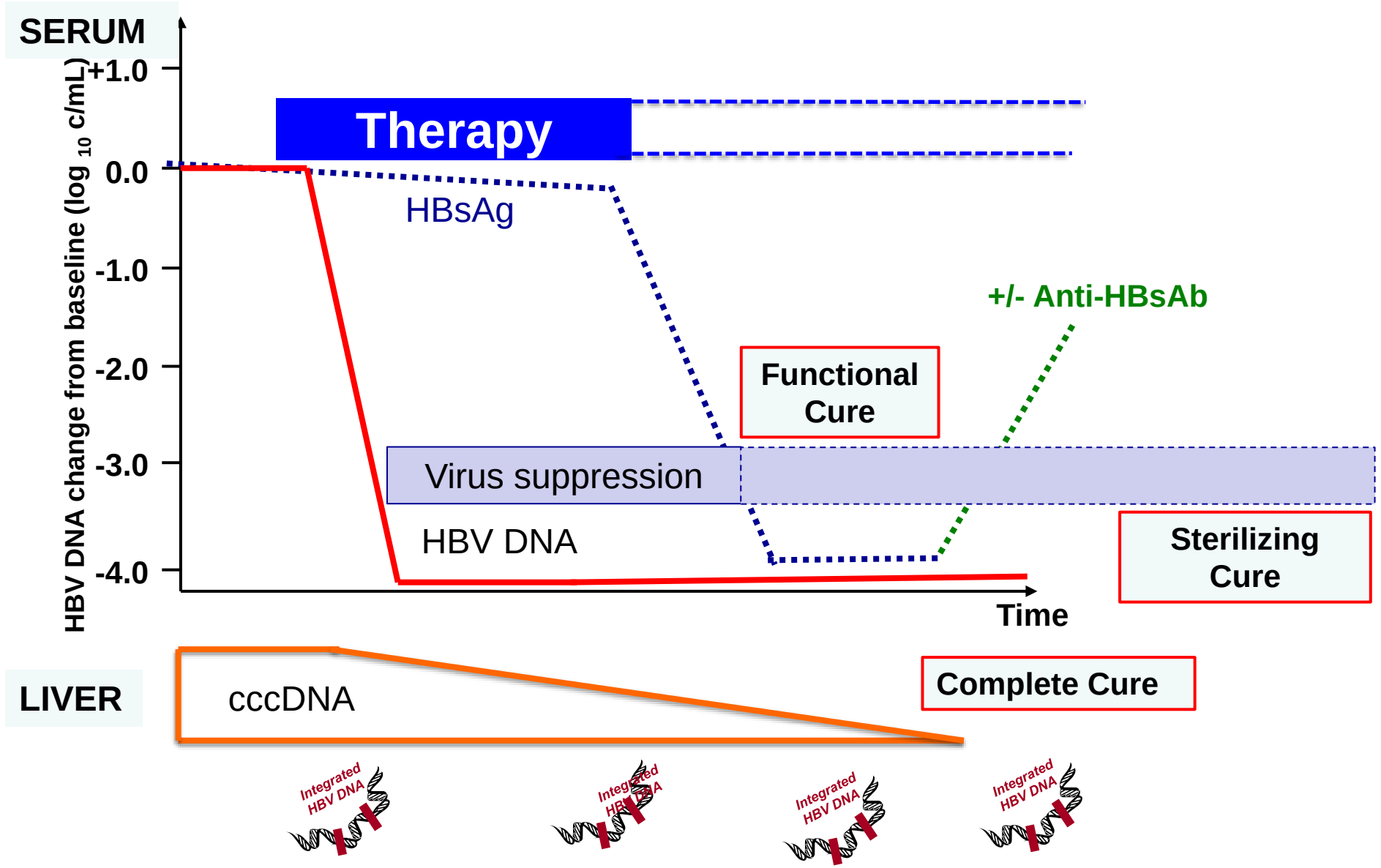
Defective B cell responses

Inefficient innate response

Defective immune responses

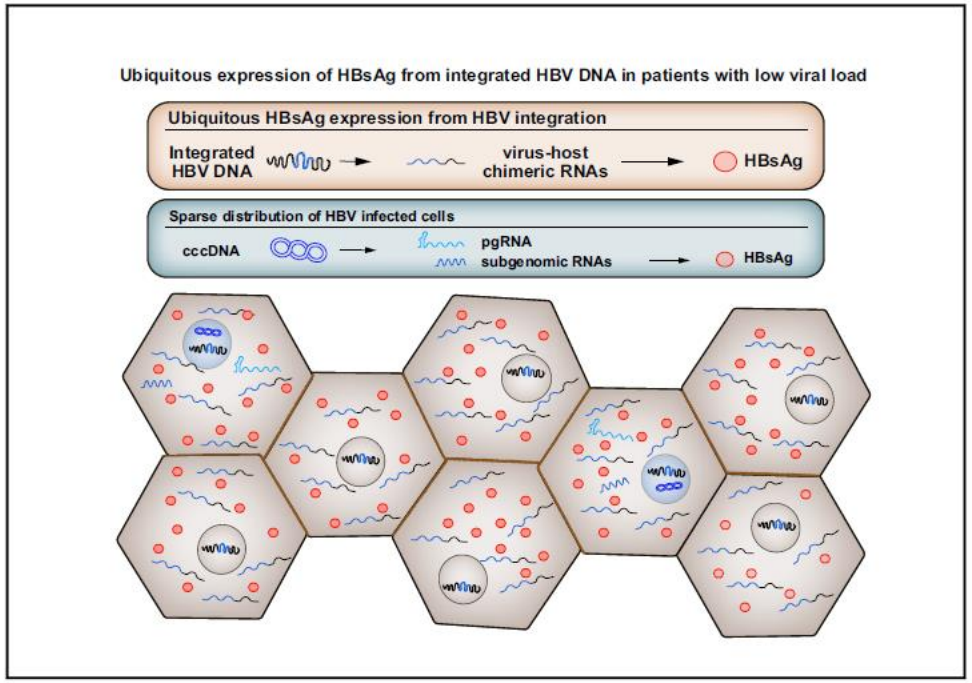
Revill, Testoni, Locarnini, S. & Zoulim, F. et al.Nat. Rev. Gastroenterol. Hepatol. 2016
Revill et al, Lancet Gastroenterol and Hepatol, 2019

Goals of future therapies to cure HBV infections



Lok et al, Hepatology / J Hepatol joint publication, 2017; Testoni et al, Sem Liver Dis, 2017.

Ubiquitous expression of HBsAg from integrated HBV DNA in patients with low viral load



- A unique set of liver biopsies from patients with HBeAg-negative chronic hepatitis B infection was studied.
- HBV RNA and antigen expression are ubiquitous in the liver despite low viremia.
- Levels of the viral transcriptional template cccDNA are not sufficient for ubiquitous HBV RNA and antigen expression.
- Intrahepatic viral DNA and RNA levels are consistent with wide-spread HBV integration.

…questioning the clinical utility of HBsAg as a surrogate marker for viral replication

Meier MA, et al J Hepatology 2021:75:840-47

Transcriptionally active HBV integration contribute to residual intrahepatic HBsAg in patients with functional cure

Objective

Explore the potential of HBV integration in patients with functional cure.

Methods

HBV capture sequencing and transcriptome sequencing were performed for HBV integration analysis and immunohistochemis-try of intrahepatic HBsAg was performed in patients with functional cure.

Main Findings

The positive HBsAg hepatocytes existed in 21.1% of patients with functional cure and we found that intrahepatic residual HBsAg was mainly derived from transcriptionally active HBV integration in five patients with functional cure (Figure 1).

Conclusions

Transcriptionally active HBV integration contribute to the residual intrahepatic HBsAg in patients with functional cure.

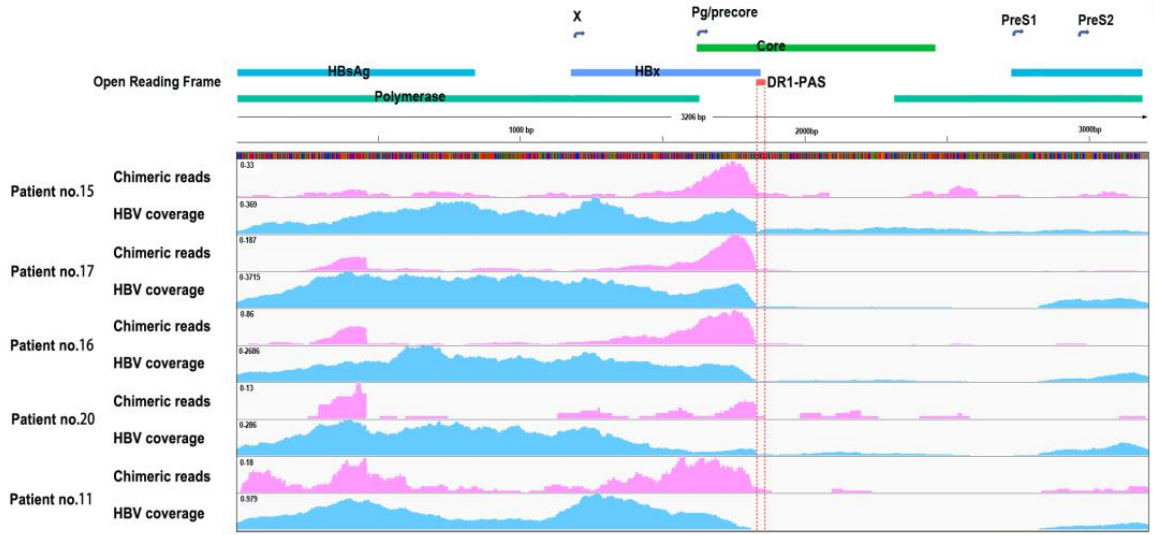


Figure 1. Five profiles of functionally-cured patients with immunohistochemical HBsAg positivity mapped to the HBV reference genome.

The profiles in pink show the coverage of chimeric reads, which represent the HBV integration events. The profiles in blue show the HBV RNA reads coverage. The location of the direct repeats 1 (DR1) to polyadenylation signal (PAS) (orange dashed line) is indicated.

Gao N, et al., Abstract 37.

AASLD The Liver Meeting®

HBsAg/Anti-HBs complex levels persists up to 13 years after HBsAg loss

Objective

To examine the immune complex (IC) kinetics prior to and after spontaneous and treatment-induced HBsAg loss using a novel assay.

Methods

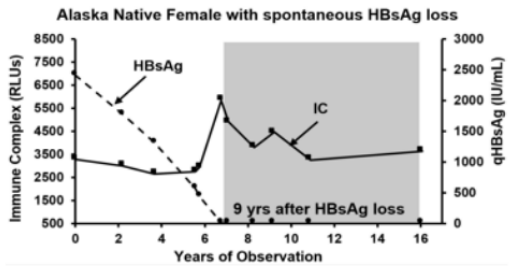
Retrospective study: 31 HBeAg (-) CHB subjects (13 Alaska natives, 18 US tertiary center patients) with spontaneous or nucleos(t)ide analog (NA)-induced HBsAg loss.

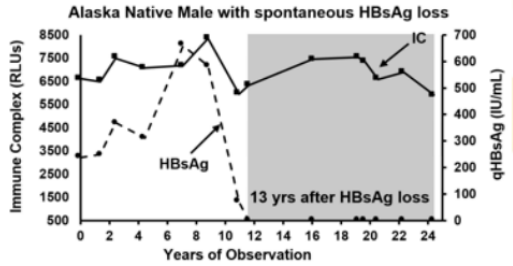
Main Findings (see Figure for representative patients)

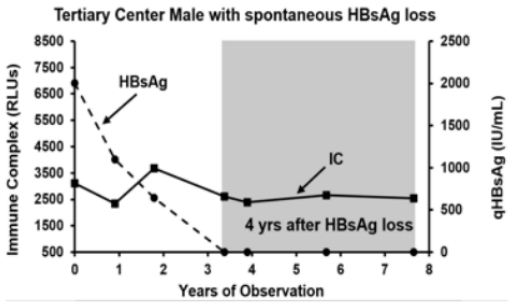
17 (55%) achieved HBsAg seroconversion with anti-HBs (+). Regardless of the anti-HBs status, IC continued to be detectable after HBsAg loss.

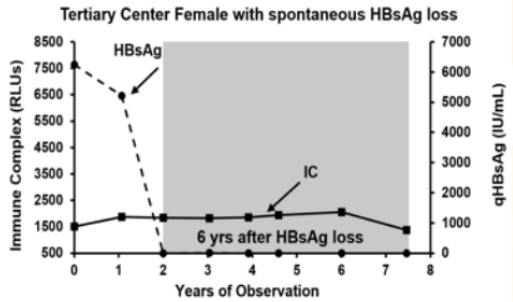
Conclusions

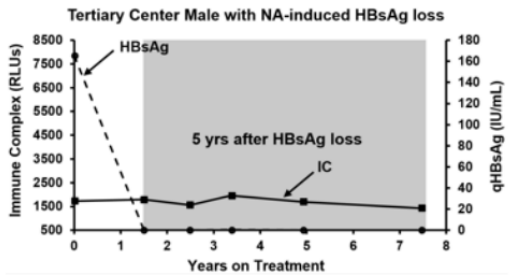
- Immune complexes are present for prolonged periods after both spontaneous and NA-induced functional cure.
- It is possible that HBsAg continues to be generated from integrated HBV DNA to extend HBsAg/anti-HBs immune complex production over time.

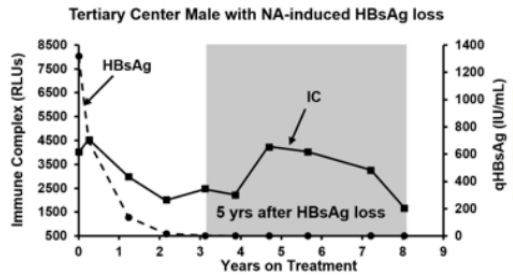








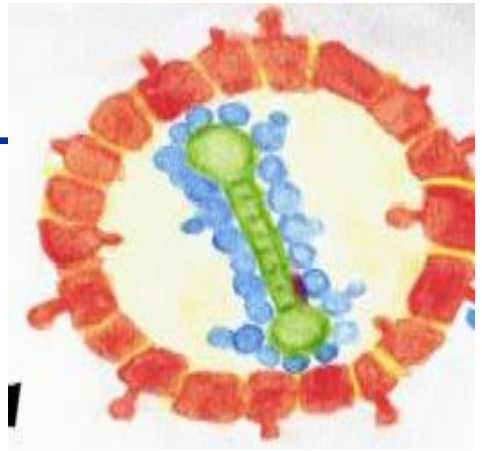




Ali MJ, et al., Abstract 38.

AASLD The Liver Meeting®

Hepatitis D (delta) Virus



- The «Delta agent» was discovered in 1977 by Mario Rizzetto
- Defective virus that needs HBsAg for its propagation
- 10-20 million individuals are anti-HDV positive
- Causes the most severe form of chronic viral hepatitis

  More rapid progression to liver cirrhosis and liver cancer; 5-7x more likely to develop cirrhosis and HCC vs HBV

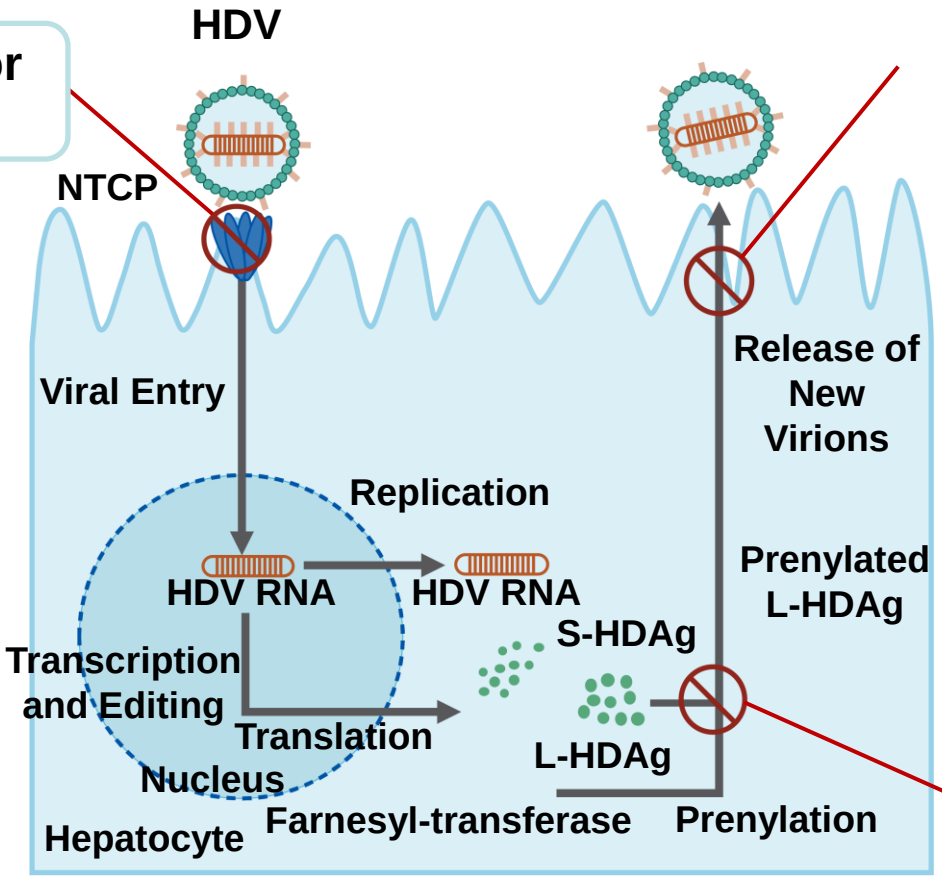
- Current standard anti-HDV therapy: NUC not effective, PegIFNα effective in only 20% of the patients (not EMA or FDA approved)
- New therapies are needed

Calle Serrano et al, Semin Liver Dis. 2012 Lempp et al, Nat Rev. 2016

Therapeutic Targets for HDV Infection

Entry Inhibitor
Bulevirtide

Inhibitors of HBsAg Release (NAPs)
REP-2139
REP-2165



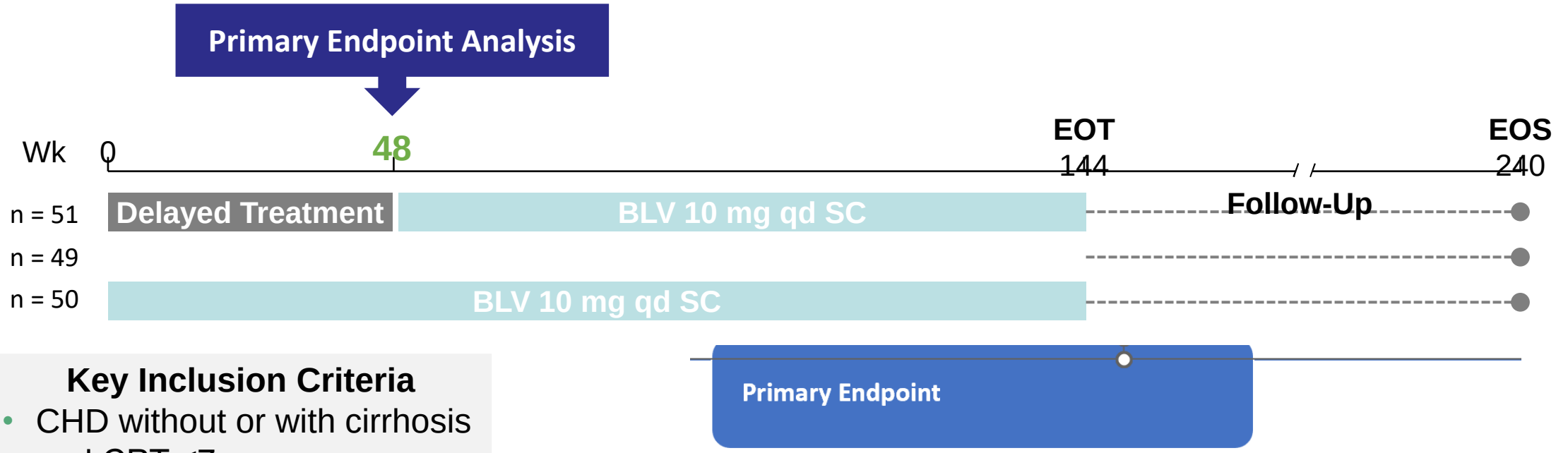
Immunomodulators
PEG-IFN-λ
PEG-IFN-α

Prenylation Inhibitor
Lonafarnib

PEG-IFN-λ: pegylated interferon lambda; L-HDAg: large form HDV antibody; NAP: nucleic acid Polymer.
Loureiro D et al. *Liver Int*. 2021;41:30-37.

MYR301: Study Design

Multicenter, open-label, randomized phase III trial conducted in 4 countries (Germany, Italy, Russian Federation, and Sweden) including 150 patients with CHD



Key Inclusion Criteria

- CHD without or with cirrhosis and CPT ≤7
- ALT >1x to <10x ULN
- Platelets ≥60,000 cells/mm^3

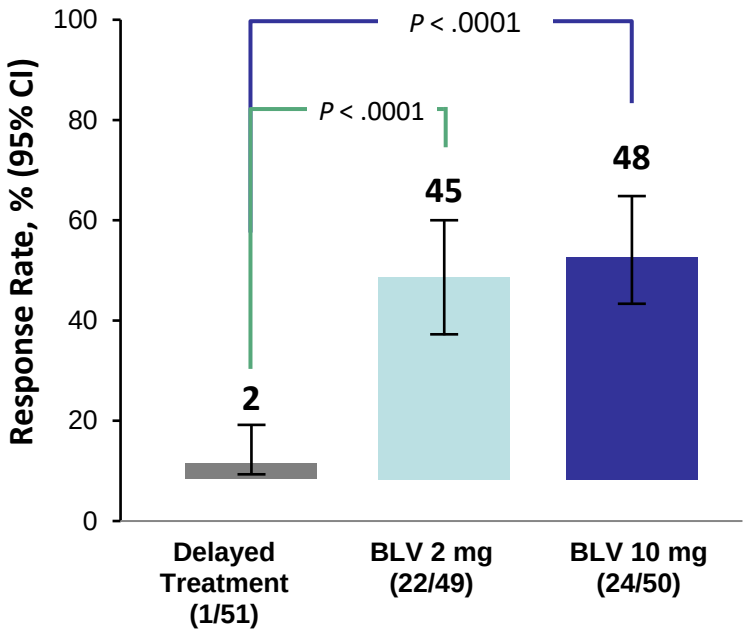
- Combined response at Wk 48: HDV RNA undetectable *or* decrease by ≥2 $\log_{10}$ IU/mL from BL *and* ALT normalization (FDA draft guidance for development of HDV treatment)

BLV: bulvirtide; EOS: end of study; EOT: end of treatment; qd: once daily.

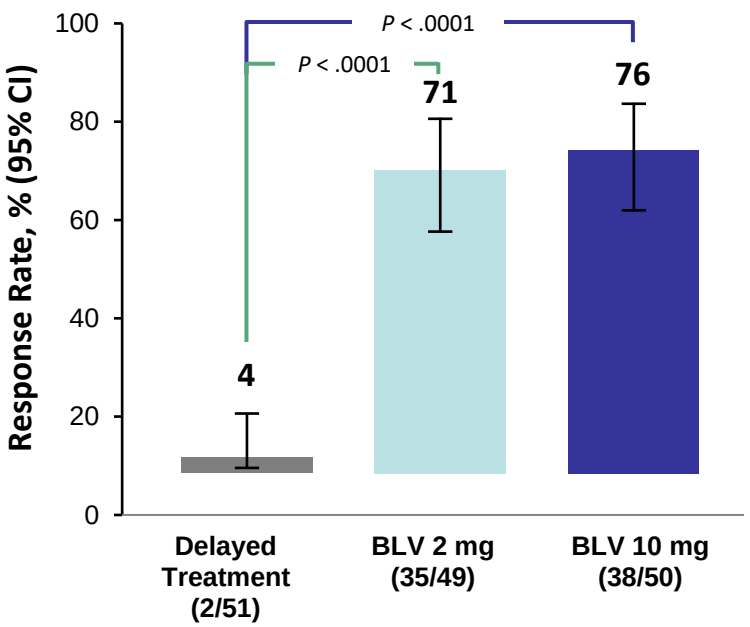
Wedemeyer H et al. International Liver Congress. 2022. Oral 509; ClinicalTrials.gov Identifier: NCT03852719. https://clinicaltrials.gov/ct2/show/NCT03852719. Accessed November 1, 2022.

MYR301: Response at Week 48

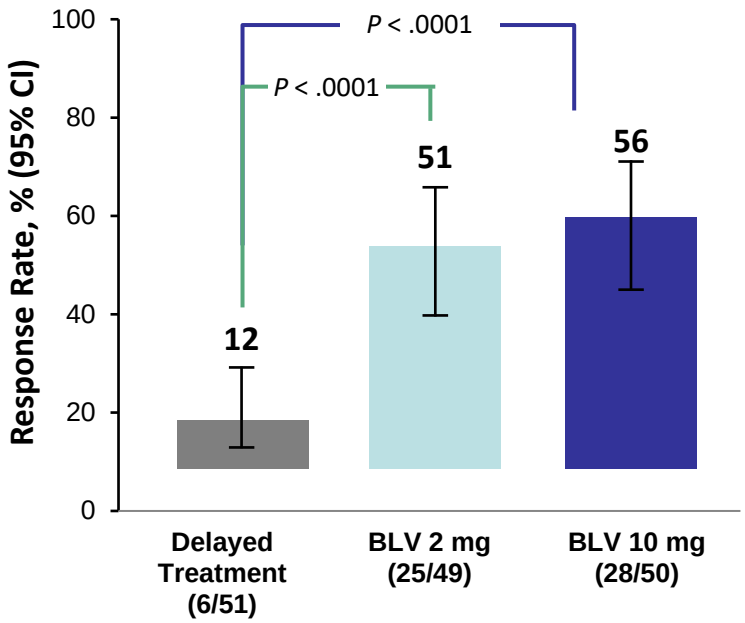
Primary Endpoint



HDV RNA Response



Biochemical Response



Wedemeyer H et al. International Liver Congress. 2022. Oral 509.

MYR301: Safety

BLV Monotherapy in Patients With Chronic Hepatitis Delta, Wk 48 Analysis

		Delayed Treatment, n = 51	BLV 2 mg, n = 49	BLV 10 mg, n = 50
Any AE		39 (77)	40 (82)	44 (88)
Any Grade 3-4 AE		3 (6)	5 (10)	4 (8)
Any SAE		1 (2)[a]	2 (4)[b]	1(2)[c]
Any AE leading to withdrawal of BLV		0	0	0
Any AE related to BLV		0	24 (49)	36 (72)
Death		0	0	0
AEs of Interest[d]	Headache	0	9 (18)	10 (20)
	Dizziness	0	2 (4)	2 (4)
	Nausea	2 (4)	3 (6)	4 (8)
	Pruritis	0	6 (12)	8 (16)
	Fatigue	1 (2)	5 (10)	8 (16)
	Injection site reactions[e]	0	8 (16)	15 (30)

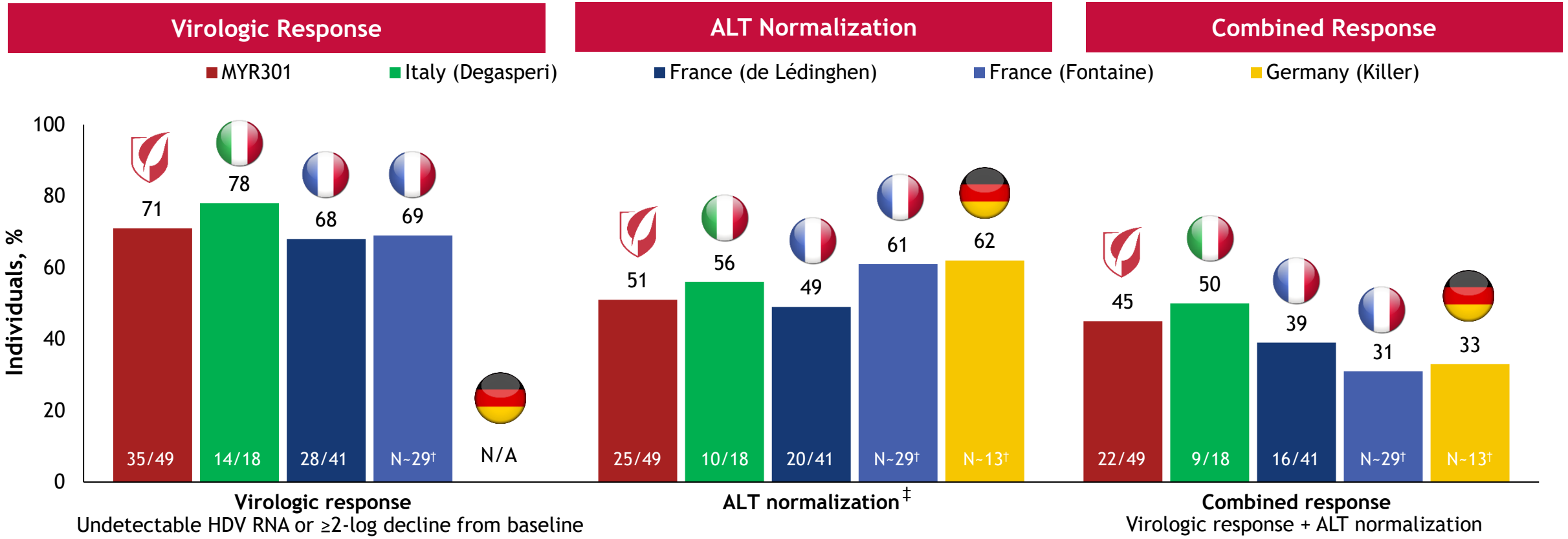
- No SAEs related to BLV or AEs leading to discontinuation of study drug
- Asymptomatic elevations in total serum bile acids observed in BLV groups
- Injection site reactions were mild to moderate and occurred at a higher frequency with BLV 10 mg
- **No case of Grade 3 or 4 elevation in bile acids**

[a]Cholelithiasis (n = 1), COVID-19 (n = 1); [b]Asthenia and depression (n = 1), foot fracture (n = 1); [c]COVID-19 pneumonia (n =1); [d]AEs with higher frequencies in BLV groups compared to delayed treatment; [e]Grouped term including injection site reaction, injection site erythema, injection site pruritis, injection site swelling, injection site pain, injection site haematoma, injection site rash, injection site abscess, injection site dermatitis, injection site irritation. [f]Grade >3 AEs: 1 participant each, BLV 10 mg: COVID-19, leukopenia, pneumonia; BLV 2 mg foot fracture, neutrophil count decreased, osteopenia, depression; Grade >3 AEs related to BLV: 1 participant each, BLV 10 mg: thrombocytopenia, neutropenia, leukopenia; BLV 2 mg: neutrophil count decreased.

AE: adverse event; SAE: serious adverse event.

Wedemeyer H et al. International Liver Congress. 2022. Oral 509.

BLV 2 mg monotherapy in CHD: efficacy at week 48 MYR301 and RWD Sets



Week 48 RWD support the efficacy of BLV 2 mg observed in MYR301

*NOT HEAD-TO-HEAD COMPARISONS. †n/N are not provided/unclear in the source document; ‡See slide notes for ALT cutoff values. BLV, bulevirtide; RWD, real-world data.

1) . Wedemeyer H, et al. EASL 2022. Oral #GS006; 2. Degasperi A, et al. EASL 2022. Poster #SAT429; 3. de Lédinghen V, et al. AASLD 2021. Oral #21; 4. Fontaine H, et al. EASL 2022. Oral #OS093; 5. Killer A, et al. EASL 2022. Poster #SAT345

Novel treatment options for HDV – Summary

- Novel treatment options are available for HDV
- Bulevirtide (BLV, Hepcludex) has been approved by EMA in 2020 at the dose of 2 mg/day sc for the treatment of adult patients with compensated CHD
- Phase III studies demonstrate the efficacy and safety of BLV with or without PegIFNα.
- RWD confirm efficacy and safety even in advanced compensated cirrhosis.
- Combination therapies likely to be required to cure HDV patients