Caminando hacia la curación de la Infección por el virus de la Hepatitis B

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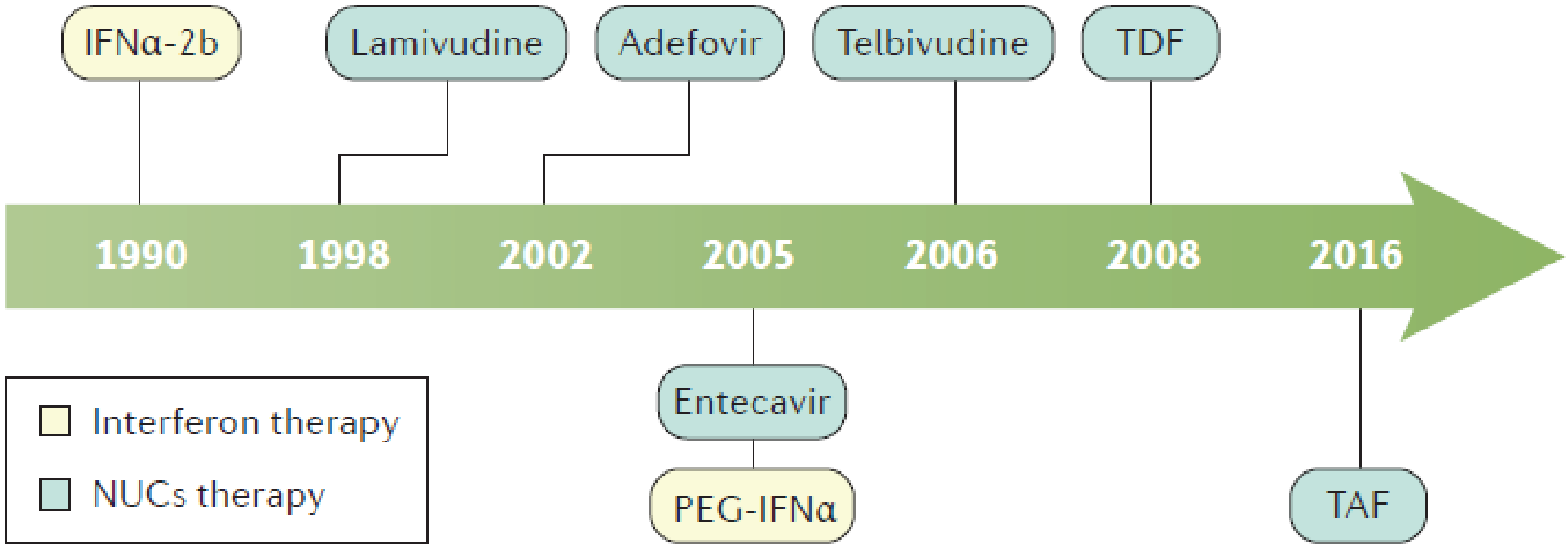
Conflicto de intereses

- AdvisorALtimmune, Abbvie, GSK, Gilead Sciences, Janssen,Roche y VIr

EL camino de la curación de la hepatitis B empezo hace años, mas de 35 años



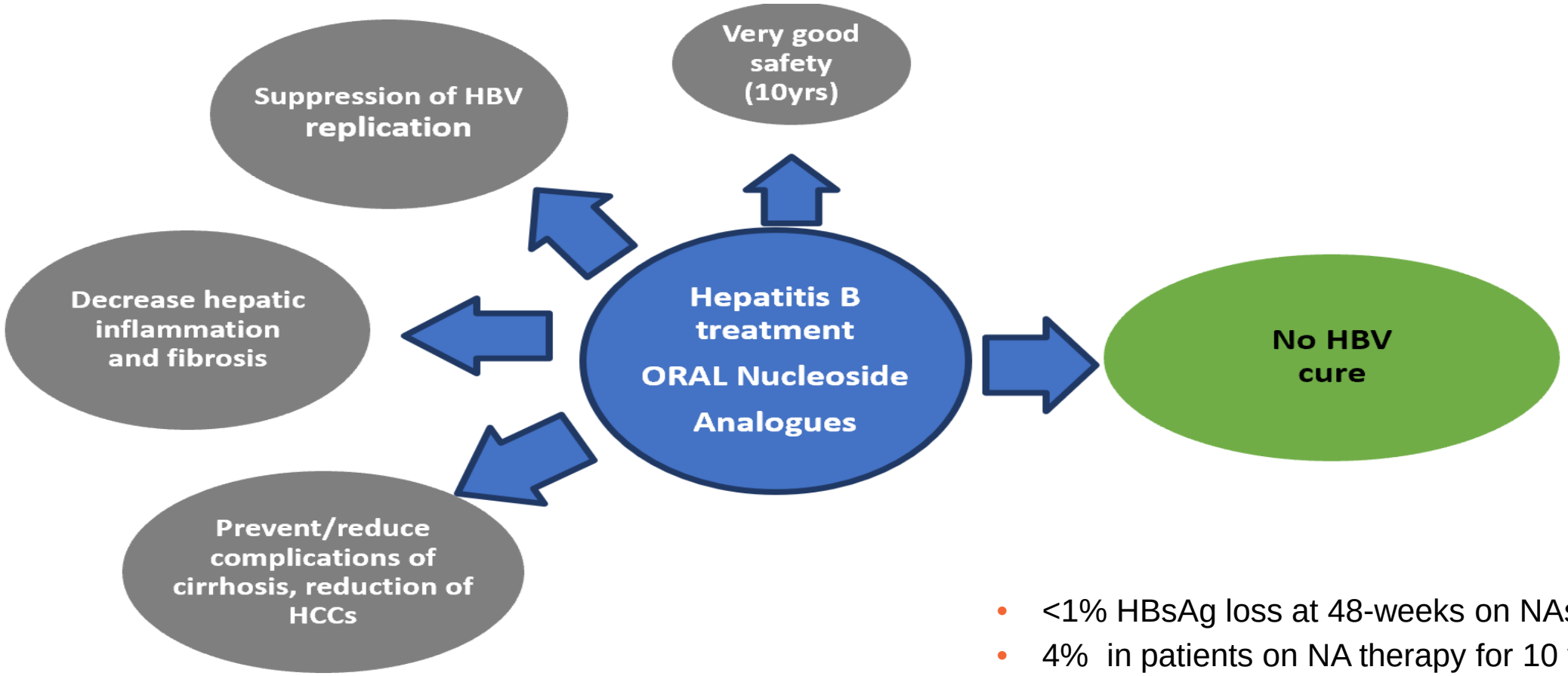
HBV: hepatitis B virus; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide, no está financiado por el SNS.

Camino de Santiago

Camino Primitivo: Interferon/Interferon Pegilado

- Candidatos: Sujeto Jóvenes, enfermedad hepática compensada y sin contraindicación al IFN
- Duración 48 Semanas
- Dificultad : Difícil
- Factores predictivos de respuesta: HBeAg positivo, Genotipo A. bajos niveles de viremia y HBsAg y valores altos de ALT
- Tasa de respuesta anual de perdida HBsAg 4-10%%

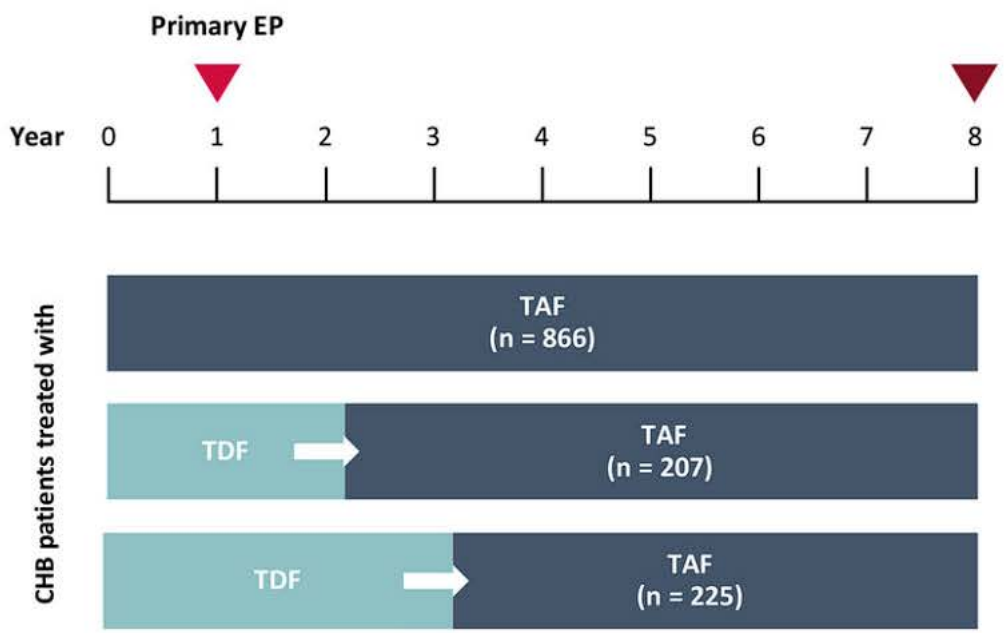
Camino Largo: NAs in the Treatment of Hepatitis B



- <1% HBsAg loss at 48-weeks on NAs therapy[1]
- 4% in patients on NA therapy for 10 years[2]

1. Marcellin P, et al. *Liver Int*. 2019;39(10):1868–1875; 2 Slaets L, et al. *Gastroenterol Hepatol.* 2020;2(3):106–116

Eight-year efficacy and safety of tenofovir alafenamide for treatment of chronic hepatitis B virus infection: final results from two randomised phase 3 trials



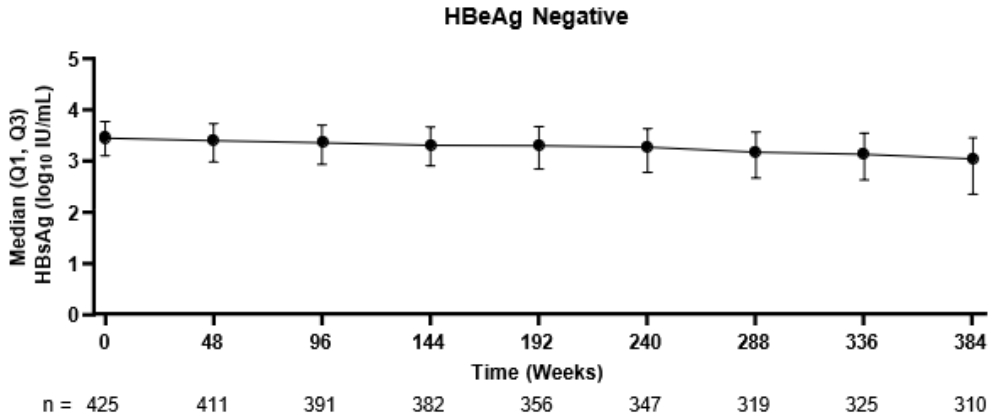
	HBV DNA <29 IU/mL		Change From Baseline: Median eGFR (mL/min)		Change From Baseline: Mean % Change Spine BMD	
	At Year 8		Year 1	Year 8	Year 1	Year 8
	M = F	M = E				
TAF (n = 866)	69% (571/832)	95% (571/600)	−1.1	−5.4	−0.6	−0.6
TDF → TAF (n = 207)	66% (117/177)	94% (117/125)	−4.1	−5.0	−2.7	−1.0
TDF → TAF (n = 225)	73% (165/225)	97% (165/170)	−5.9	−4.9	−2.1	0.8

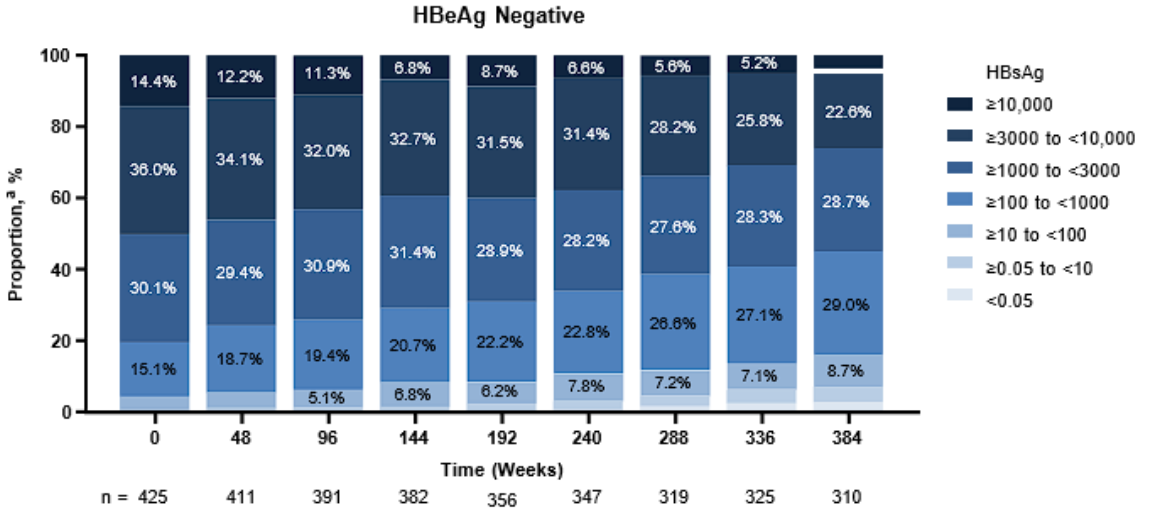
BMD, bone mineral density; CHB, chronic hepatitis B; eGFR, estimated glomerular filtration rate; EP, endpoint; HBV, hepatitis B virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; M = E, missing-equals-excluded; M = F, missing-equals-failure.

⊗ No resistance to TAF detected

Buti M et a. Alimentary Pharmacology & Therapeutics 2024

HBsAg Loss Following 8-Year TAF/TDF Treatment in CHB Patients





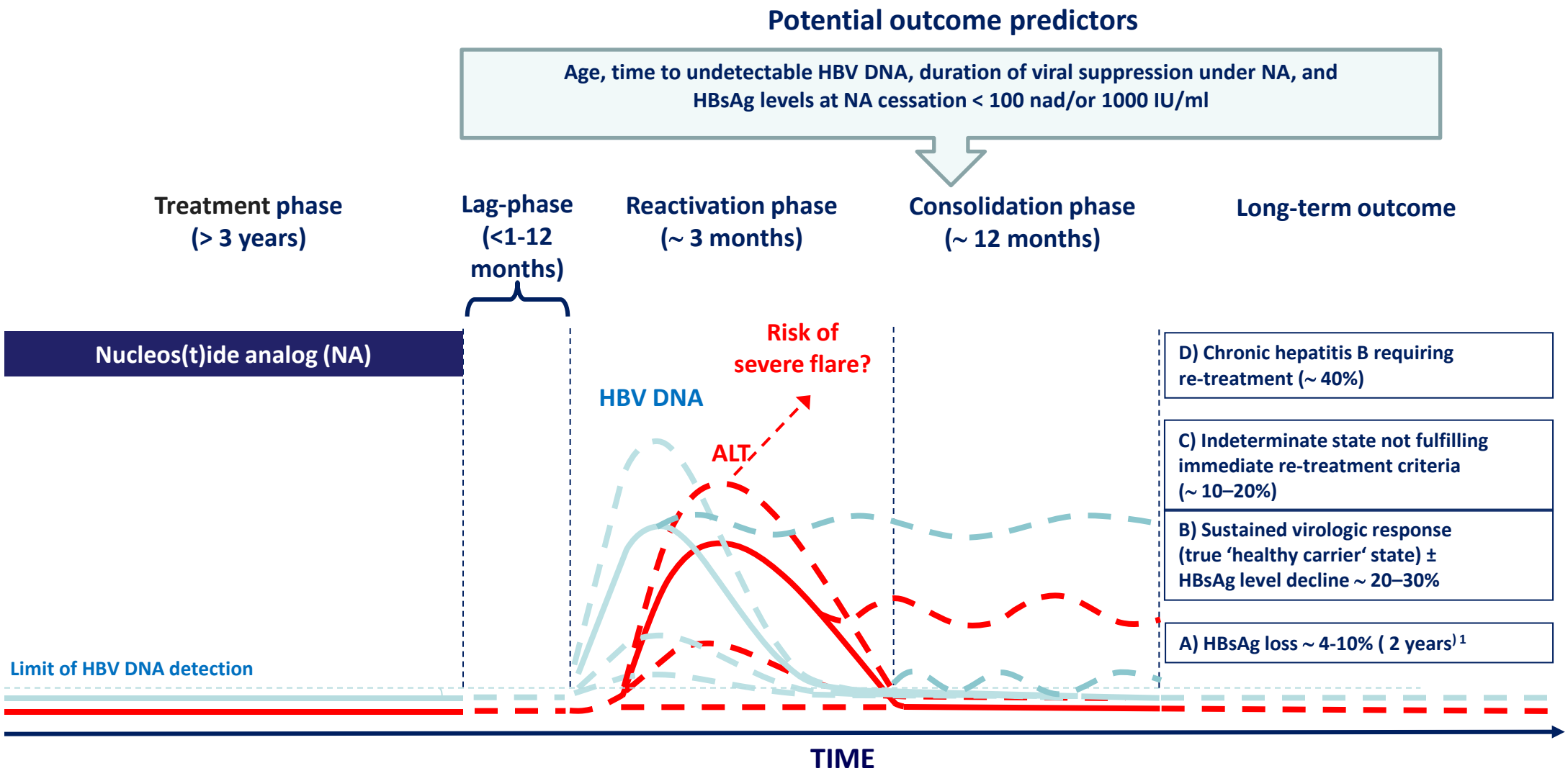
[a]Proportions of the stacked bar graph (ie, shaded regions) without a data label represent ≤5% of patients.
HBeAg, hepatitis B e antigen; **HBsAg**, hepatitis B surface antigen.

Through 8 y, most patients had slight declines in HBsAg levels (median −0.73 log10 IU/mL change from baseline)
Only 2%–3% experienced HBsAg loss and seroconversion.
Factors associated with HBsAg loss were low levels (<100UI/mL) of HBsAg at baseline and >75% decline at week 24

Heo J et al. AASLD 2024. Buti M et al EASL 2024

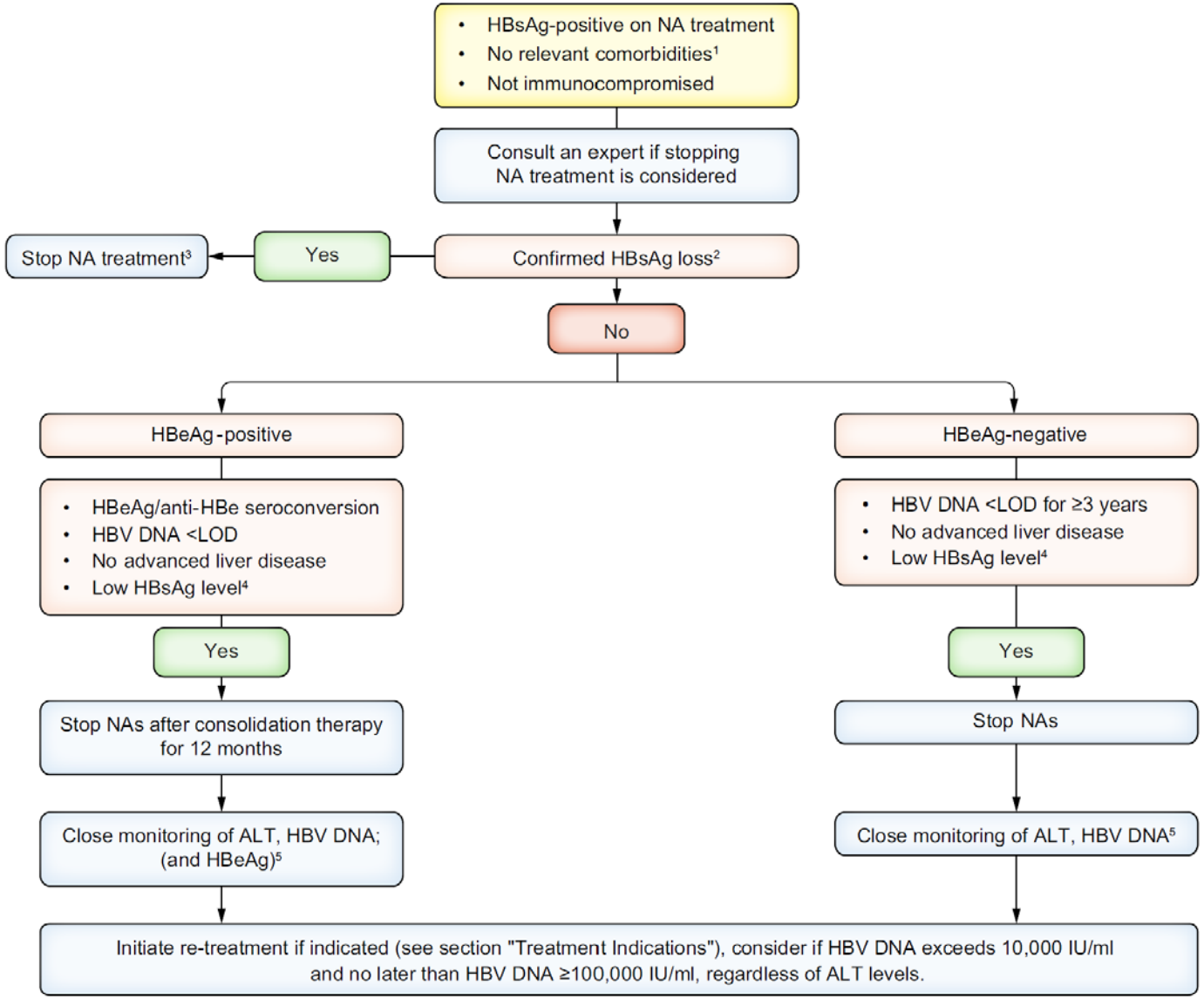
Ganar la Compostela: Discontinuacion de NUCs para lograr la perdida del HBsAg

Strategy to achieve Functional Cure
Stopping NAs before HBsAg loss in HBeAg-negative patients



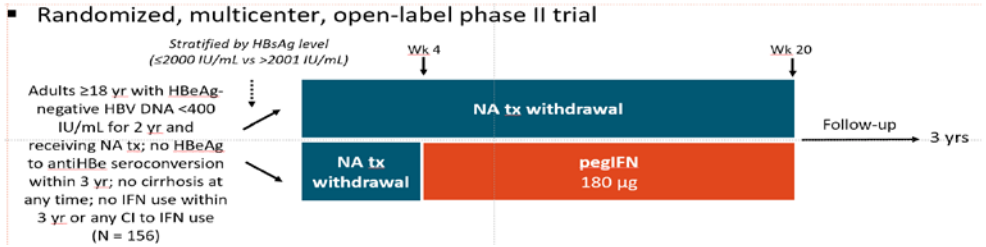
*modified Lampertico P and Berg T, Hepatology 2018*E1Dongelmans EJ et al. Jf Hepatol 2025; 82:168–170

Algorithm for stopping NA treatment.

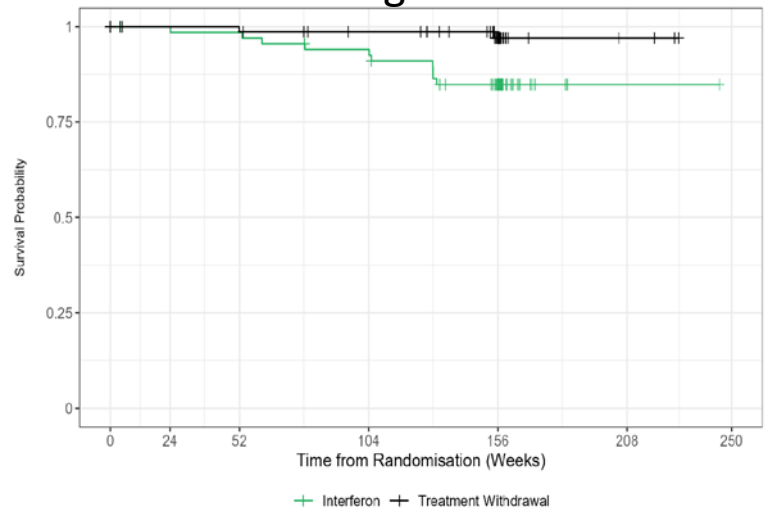


EASL Guidelines Hepatitis B 2025

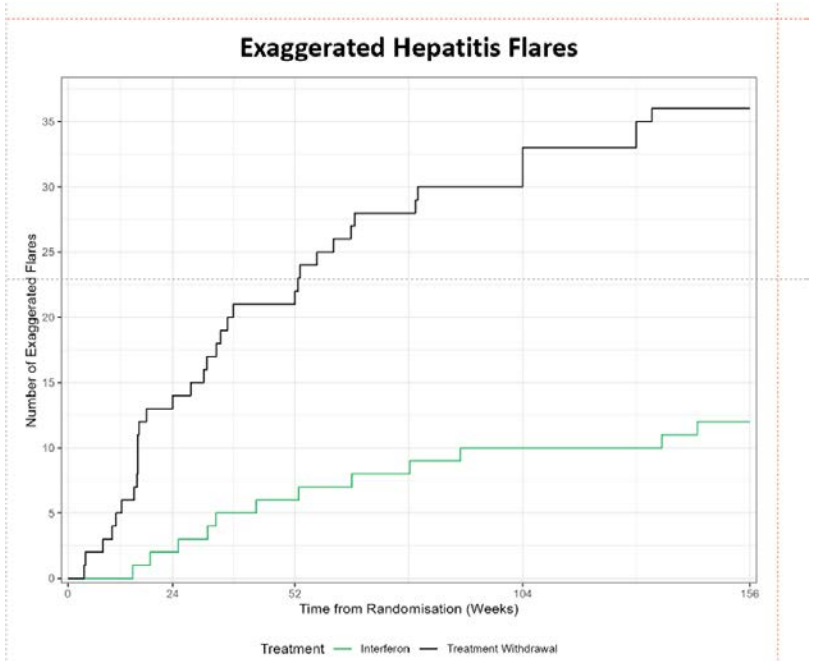
NUC-B: Effect of Adjuvant PegIFN on Functional Cure After NA Withdrawal in HBeAg-negative Chronic HBV Infection



HBsAg loss



Outcome, n/N (%)	IFN After NA Tx Withdrawal	NA Tx Withdrawal	IFN vs. Withdrawal (95% CI)	*P* value
HBsAg loss at 3 yr	9/63 (14.3)	2/67 (3.0)	OR: 5.39 (1.11-26.19)	.037
HBsAg loss and undetectable HBV DNA at 3 yr	6/62 (9.7)	1/68 (1.5)	OR: 7.55 (0.87- 65.50)	.067

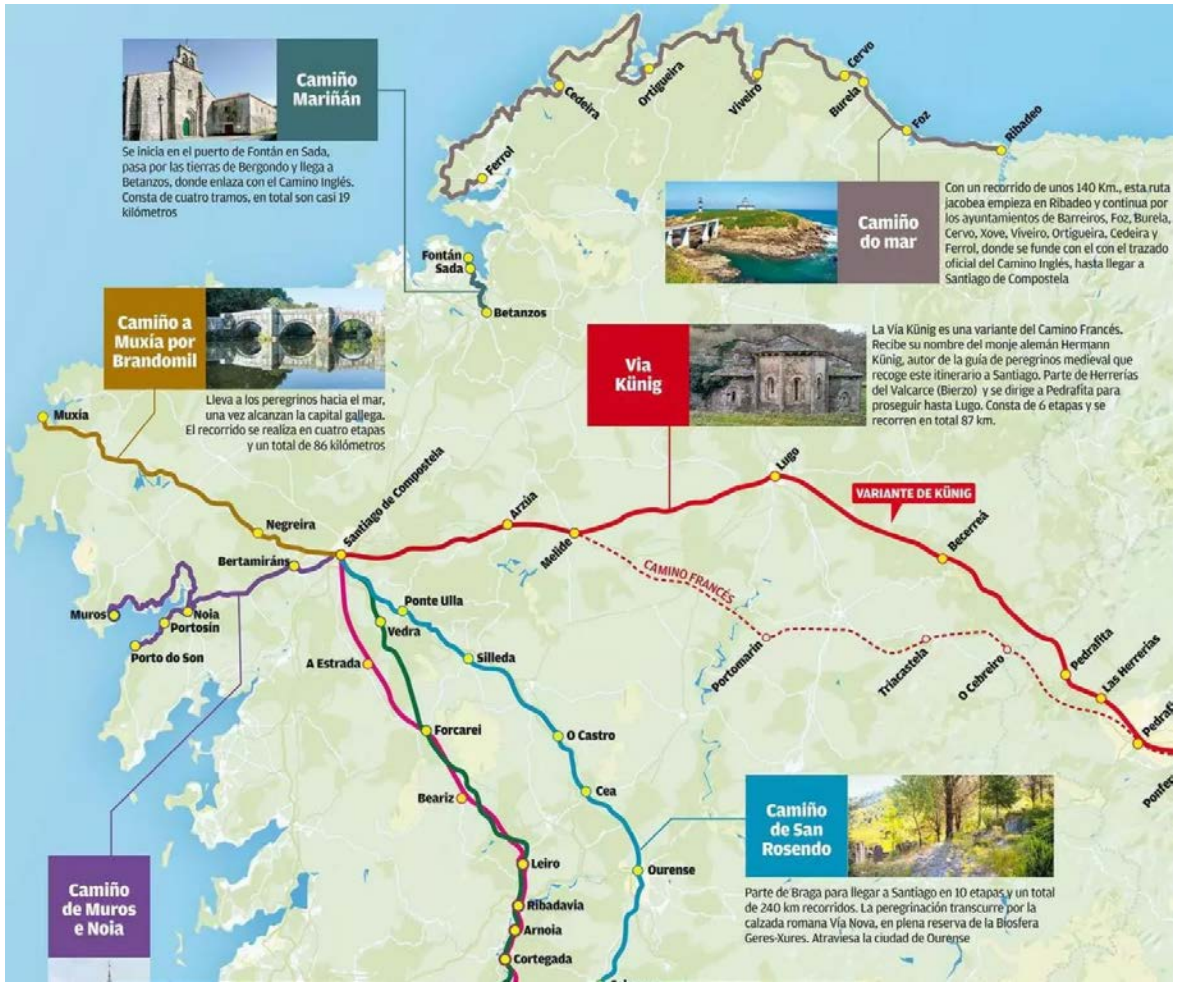


Exaggerated Hepatitis Flares	IFN After NA Tx Withdrawal (n = 67)	NA Tx Withdrawal (n = 86)
Number affected (%)	9 (13.4)	24 (27.9)
Number of events	12	36
OR (95% CI)	0.38 (0.16, 0.90)	
P value	.028	

Adjuvant pegIFN increased the rate of HBsAg loss and reduced the number of exaggerated alt flares after NUCS withdrawal

Thursz. EASL 2025. Abstr 747.

Las nuevas rutas que también quieren ser Camino de Santiago



Functional cure

- HBsAg undetectable
- Treatment Finite duration. Nas as **treatment discontinuation** is a prerequisite for functional cure[1]
- **Less monitoring** may be needed (if not cirrhotic)[1,2]
- **Lower** incidence of **complications** (e.g., HCC)[2–4]
- Reduced **social stigma**[5]

Functional cure may play a role in the strategy to achieve WHO hepatitis B elimination targets[4,6]

HCC, hepatocellular carcinoma; NA, nucleos(t)ide analogue; WHO, World Health Organization.

1. Wallace J, et al. *Viruses*. 2022;14(11):2542; 2. Broquetas T, et al. *World J Gastroenterol*. 2023;29(25):3964–3983; 3. Surana P, et al. *Antiviral Res.* 2019;168:61–67; 4. Howell J, et al. *Hepatology* 2023;78(3):976–990; 5. Tu T, et al. *Viruses.* 2020;12(5):515; 6. World Health Organization. Global hepatitis report 2024: action for access in low- and middle-income countries. Available at https://www.who.int/publications/i/item/9789240091672. Published 9 April 2024. [Accessed 15 February 2025

Novel Classes of Drugs Being Investigated

Antiviral
ASO
siRNA
CAMs
Entry inhibitors
Nucleic acid polymers (NAPs)

Immunological
PEG IFN
TLR agonists
Therapeutic vaccines
PD-1/PD-L1 inhibitors
Monoclonal antibodies

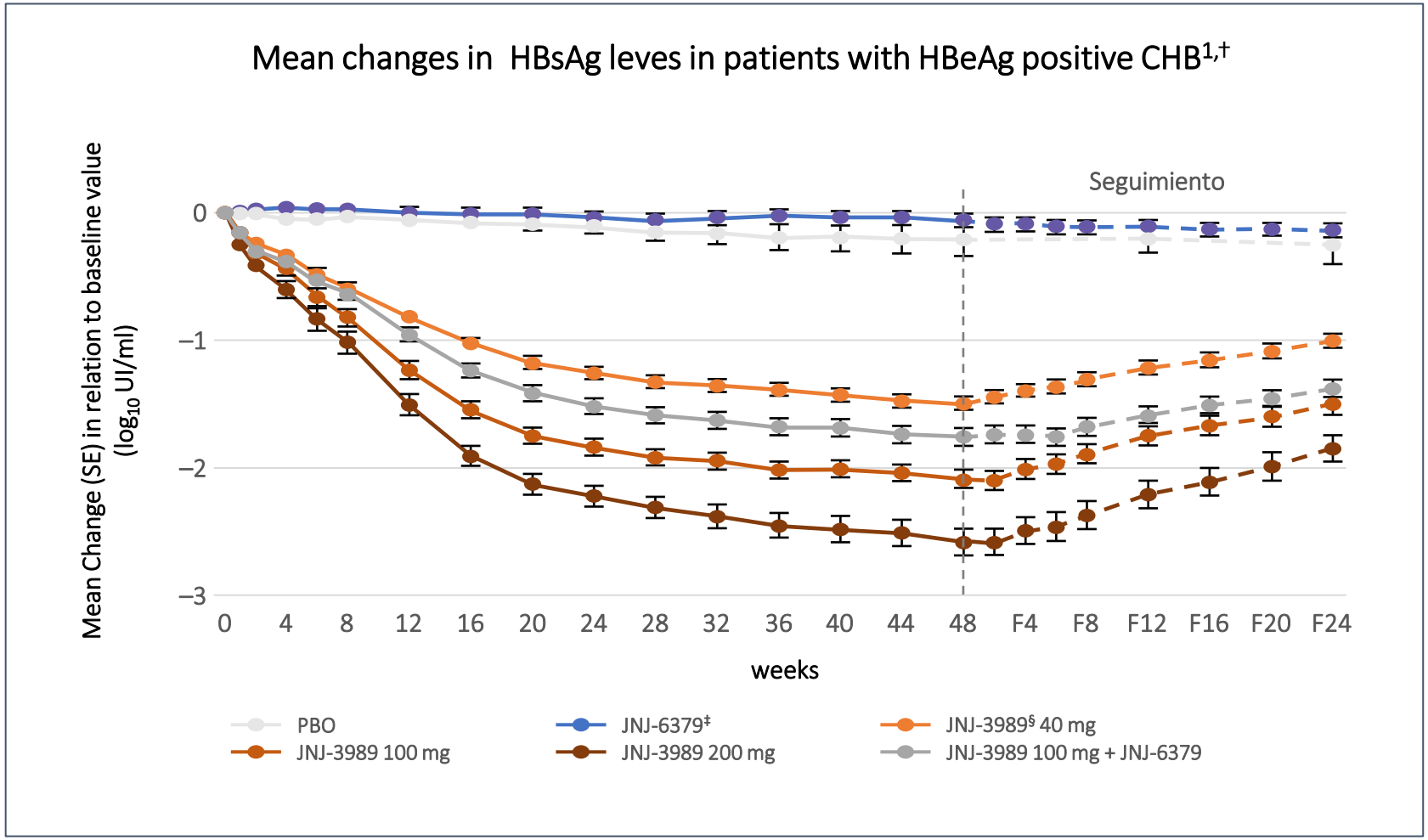
Many potential combinations: Antiviral + antiviral

Antiviral + immune modulator

Immune modulators combined

2025 Pipeline >100 drugs in preclinical, phase 1-2 clinical study and 1 in phase 3

siRNA JNJ-3989 ±Bersacapavir (CAMs) in patients with CHB: REEF-1 trial



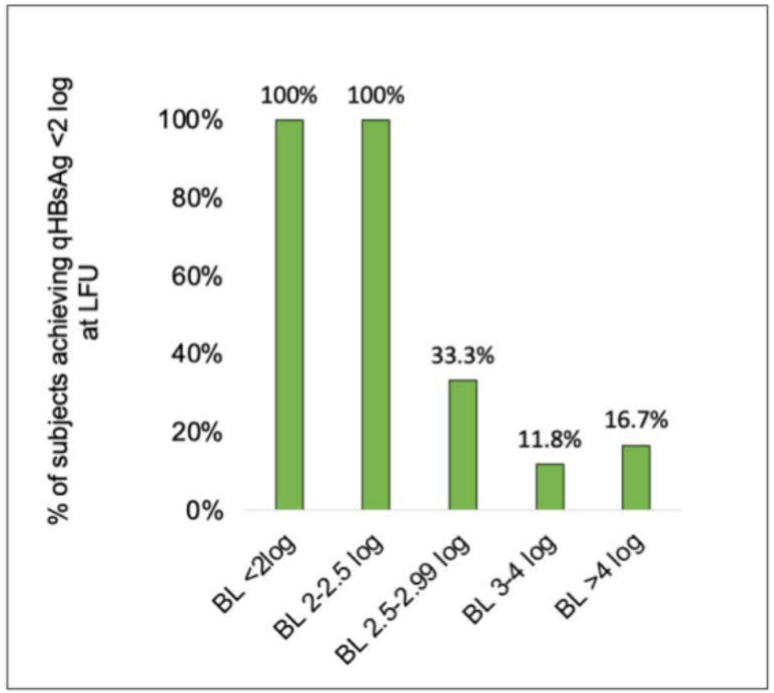
siRNA JNJ-3989

- 75 % achieved HBsAg <100 UI/ml at week 48 of therapy[1]
- No HBsAg loss at week 24 off therapy

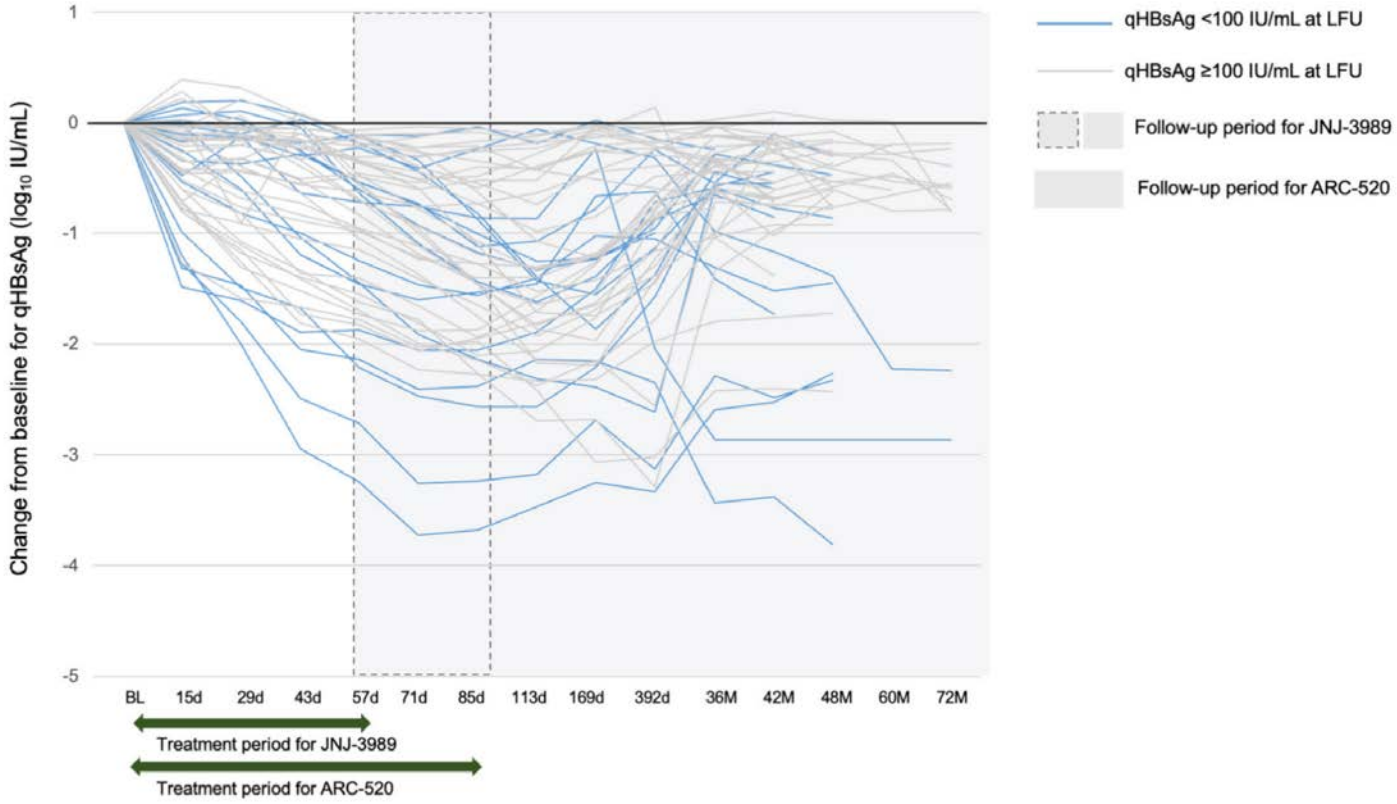
Yuen MF et al. Lancet Gastroenterol 2023;8:790-802

Long-Term HBsAg response after JNJ-3989

Baseline qHBsAg (log10IU/mL)	Sample size
< 2	2
2 - 2.49	7
2.49 - 2.99	6
3 - 4	17
> 4	6



48% and 50% of those with HBsAg <100 IU/mL and >100 IU/mL at nadir or ≤24 weeks from last dose could maintain or achieve HBsAg <100 IU/mL at LFU, respectively.

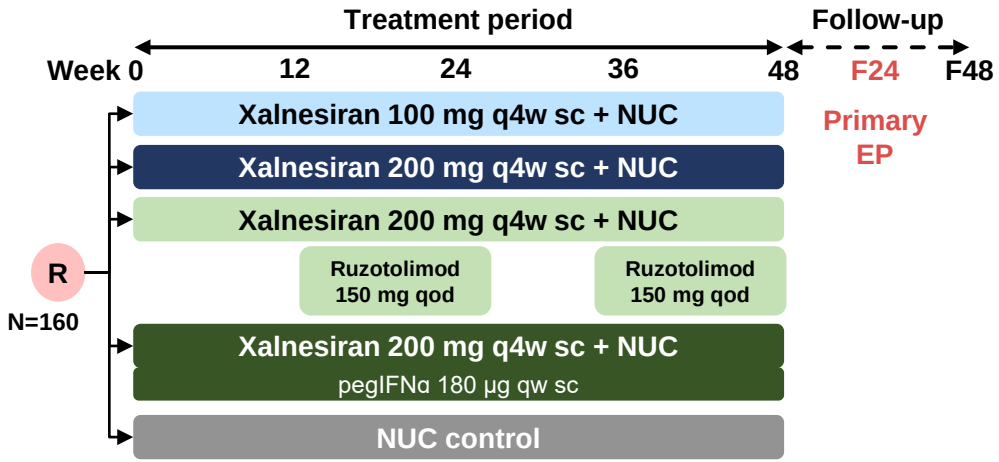


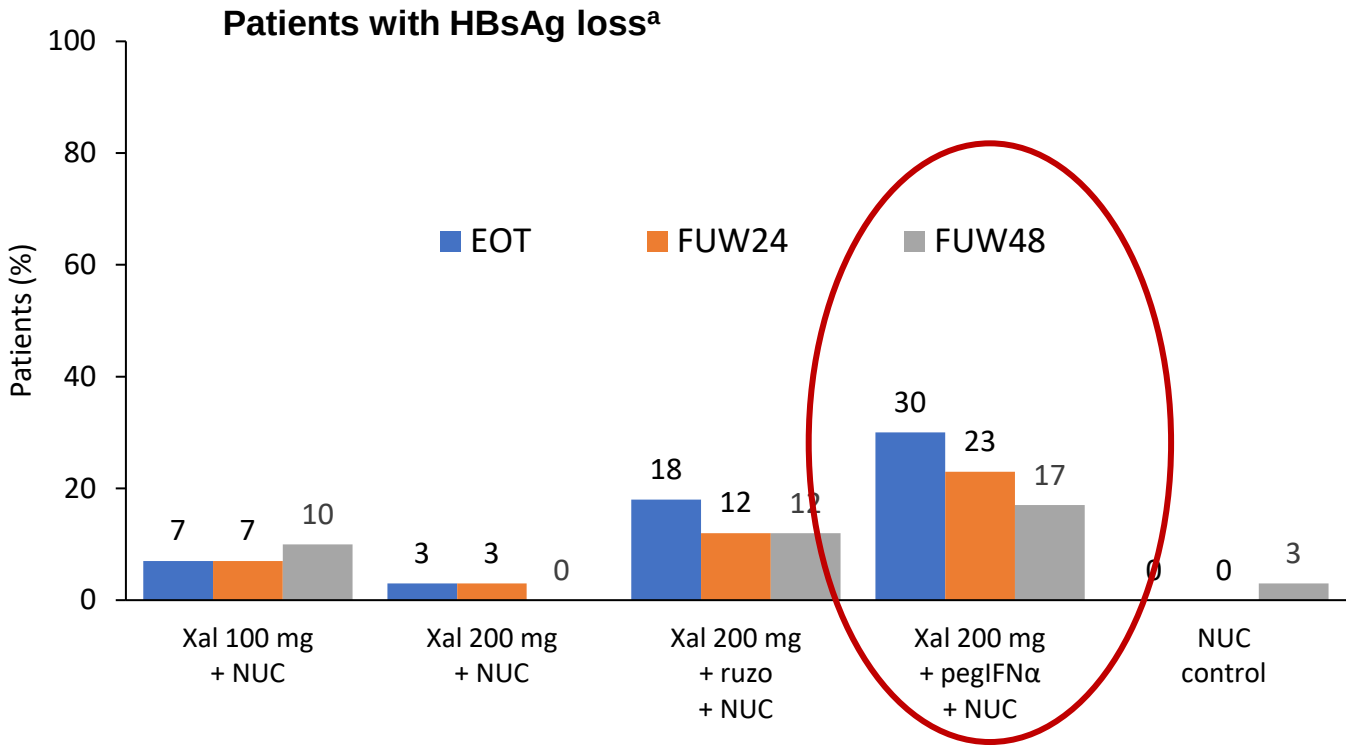
Lower baseline HBsAg, lower HBsAg at nadir and younger age were associated with better HBsAg suppression at long-term follow-up.

Mark LY et al. Gut 2025

Xalnesiran ±Immunomodulator in Chronic Hepatitis B Phase 2 randomized-controlled study

Xalnesiran ± Ruzotolimod (TLR7 agonist) ± PegIFN
No cirrhosis
NAs suppressed



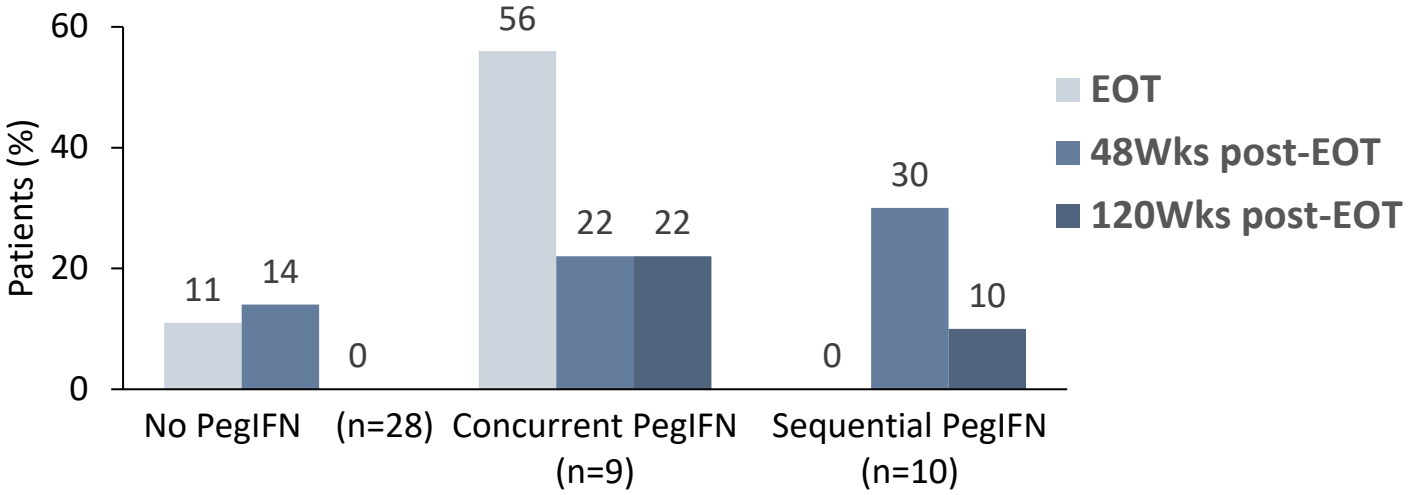


- 48-week combination of xalnesiran with ruzotolimod (12 wksX 2) / pegIFN (48 wks) is generally safe
- HBsAg loss only limited to patients with baseline HBsAg <1. 000 IU/mL
- Xalnesiran plus two immunomodulators had the highest rate of HBsAg loss

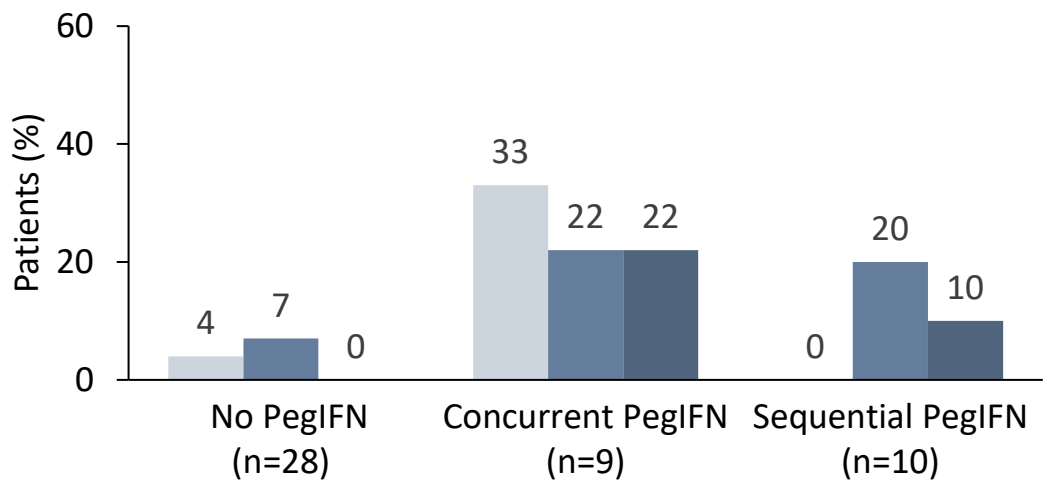
Hou J et al. N Engl J Med 2024; 391:2098-2109

Prolonged reduction of HBsAg in viral suppressed patients treated with concurrent or sequential pegIFNα with xalnesiran-based therapy: Results after 120 weeks of follow-up

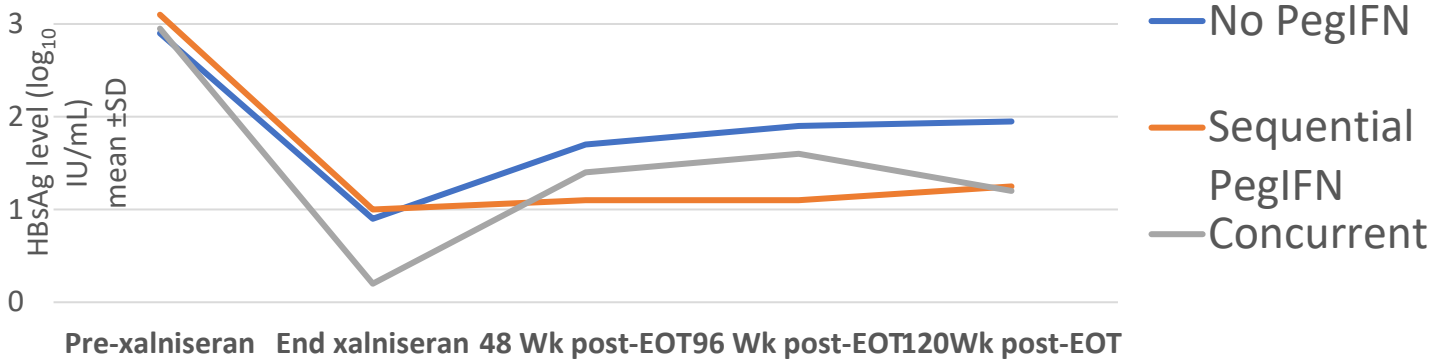
HBsAg loss during Follow-up



(HBsAg seroconversion during Follow-up



(c) Dynamic changes in HBsAg levels



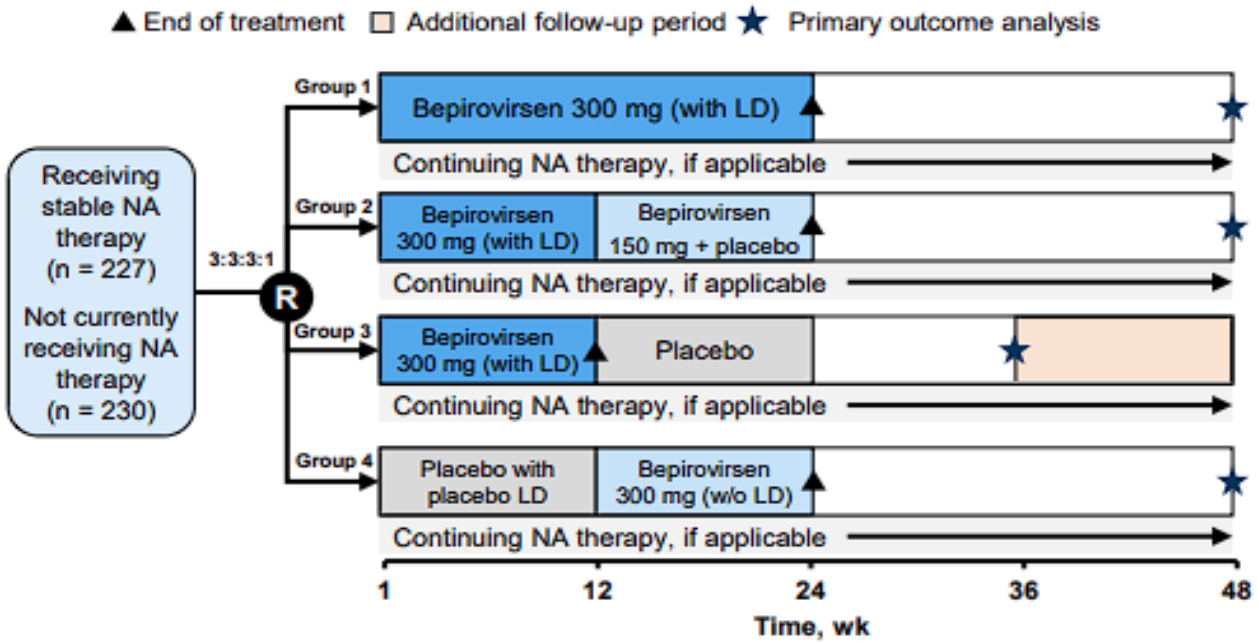
Most patients had rebound in HBsAg after EOT but this was reduced by addition of PegIFN

Concurrent PegIFN was associated with highest rates of HBsAg loss (22%) and HBsAg <100 at 120 Wks post-EOT (58%)

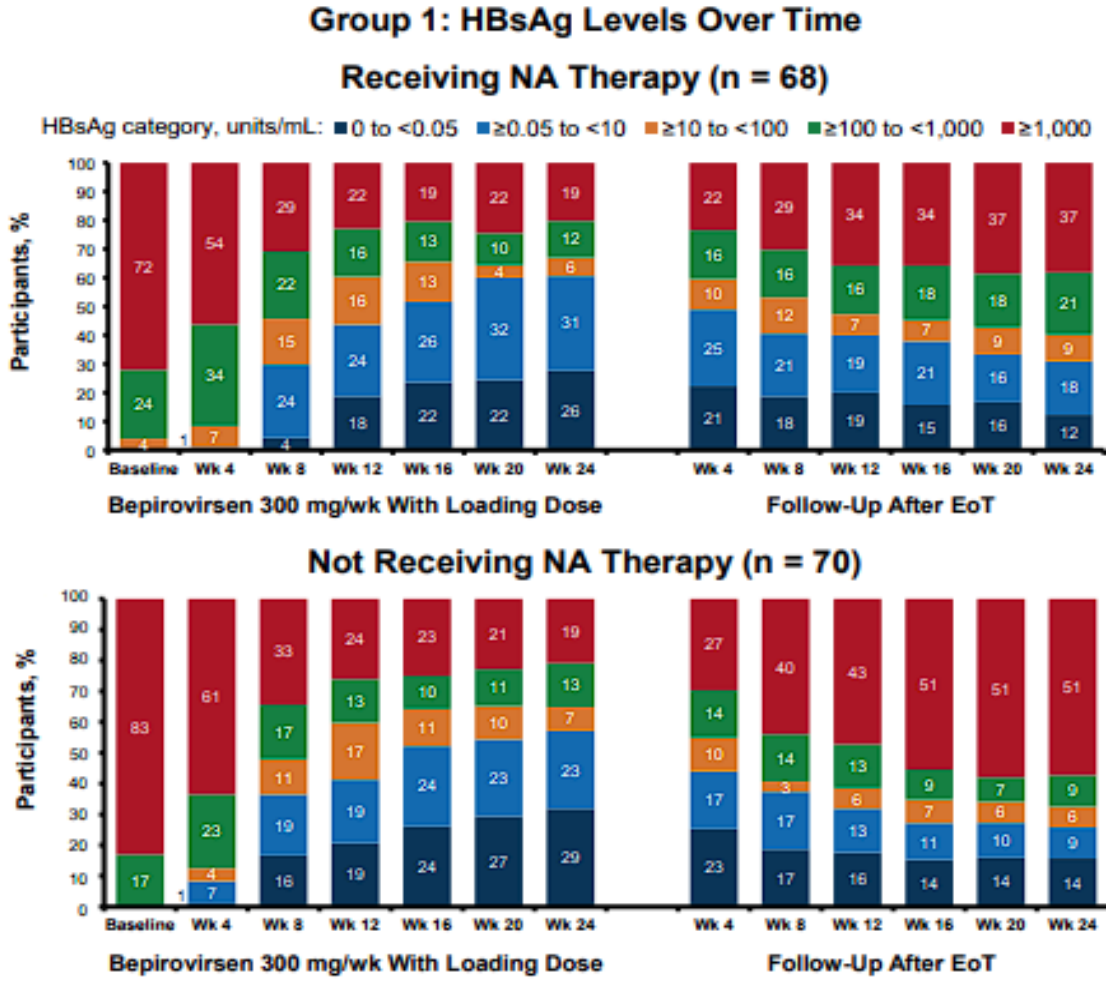
Liang X, et al. EASL 2025#LBP-021.

Bepirovirsen in Chronic HBV Infection: First Study to Demonstrate Increase in Functional Cure Rate

- Bepirovirsen is an antisense oligonucleotide that targets all HBV messenger RNAs and acts to decrease levels of viral proteins
- Composite primary outcome was (HBsAg) level below lower limit of detection and HBV DNA level below the limit of quantification at f/u wk 24



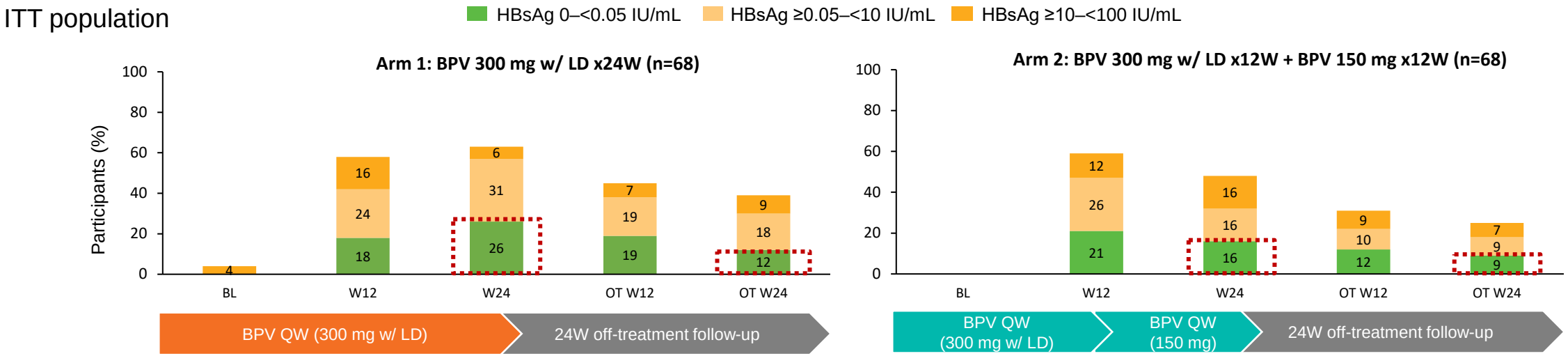
- **Primary outcome achieved in 9% of individuals receiving NA, 10% in those not on NA**
- **Baseline qHBsAg of 3,000 units/mL or less was strong predictor of response**



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

B-Clear study –Bepirovirsen in patients with CHB Results from the randomized Phase 2b in NAs suppressed

ITT population



Approximately half of participants who achieved HBsAg loss after 24 weeks of treatment maintained the response at week 24 oof therapy

Baseline HBsAg levels predicts HBsAg loss

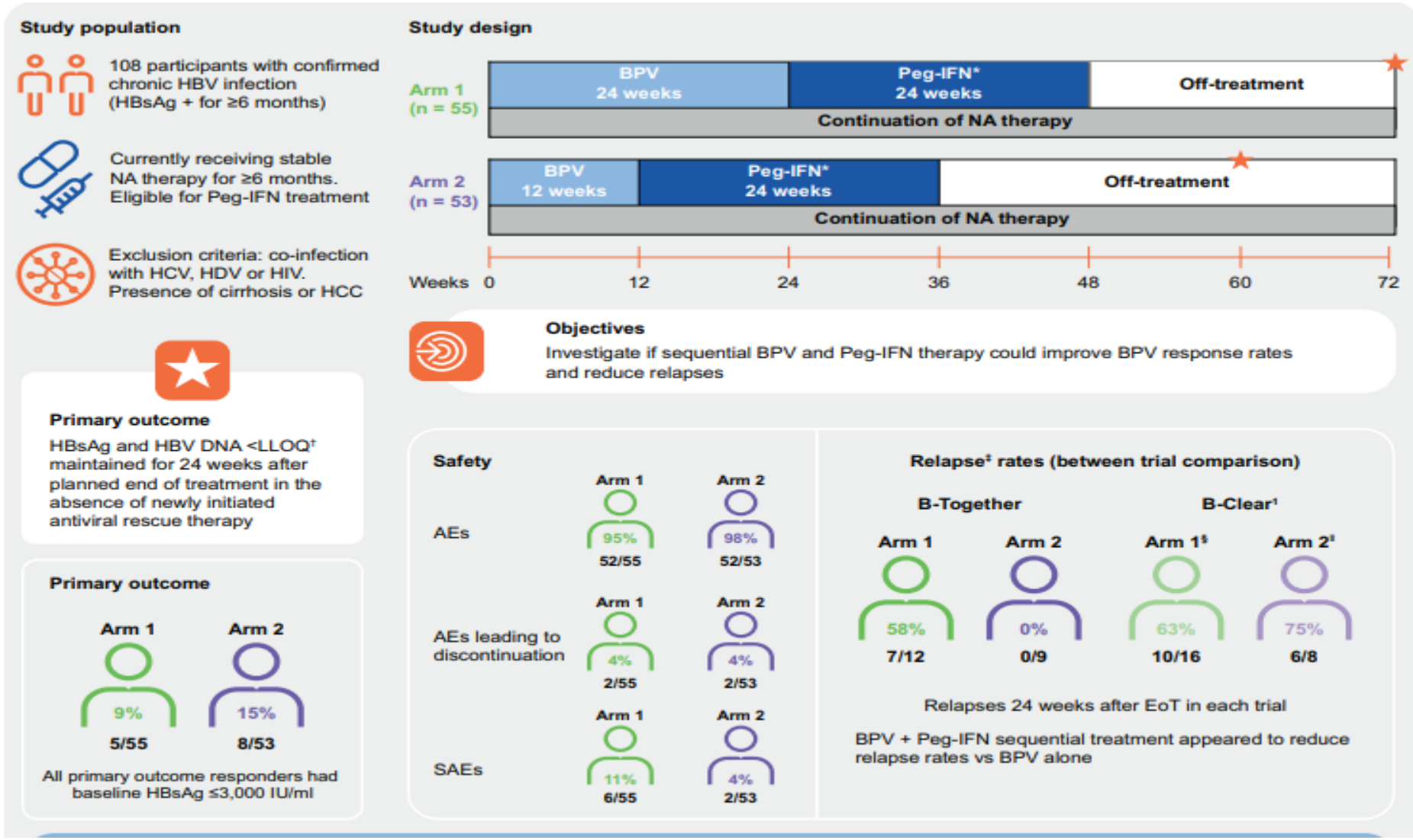
Low HBsAg level (≤3 log10 IU/ml), HBsAg loss 16% of the participants on NAs and 25% on non-NAs at the end of follow-up

High HBsAg level (>3 log10 IU/ml), HBsAg loss 6% of the participants on NUCs and 7% on non-NUCs

Percentages calculated based on the total number of participants in the ITT population, therefore totals may not add up to 100% due to missing data.
BPV, bepirovirsen; BL, baseline; HBsAg, hepatitis B surface antigen; ITT, intent-to-treat; LD, loading dose; OT, off treatment; PBO, placebo; QW, once a week; W, week; w/=with; w/o=without.

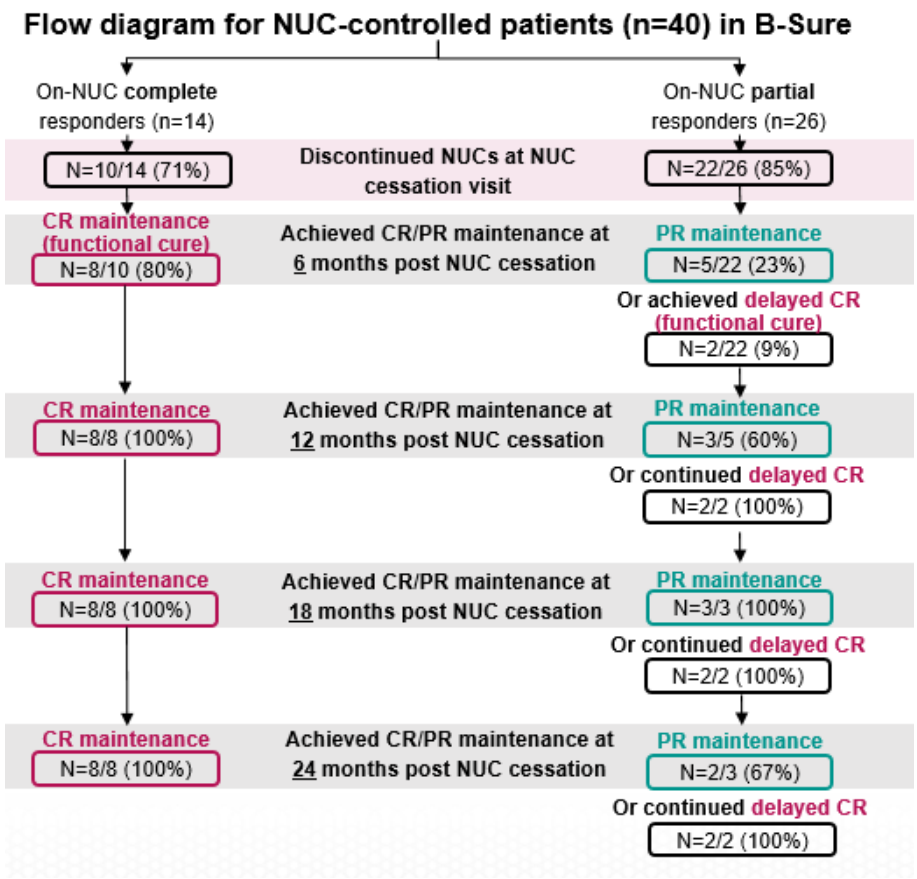
Yuen MF, et al. N Engl J Med. 2022;387:1957-1968

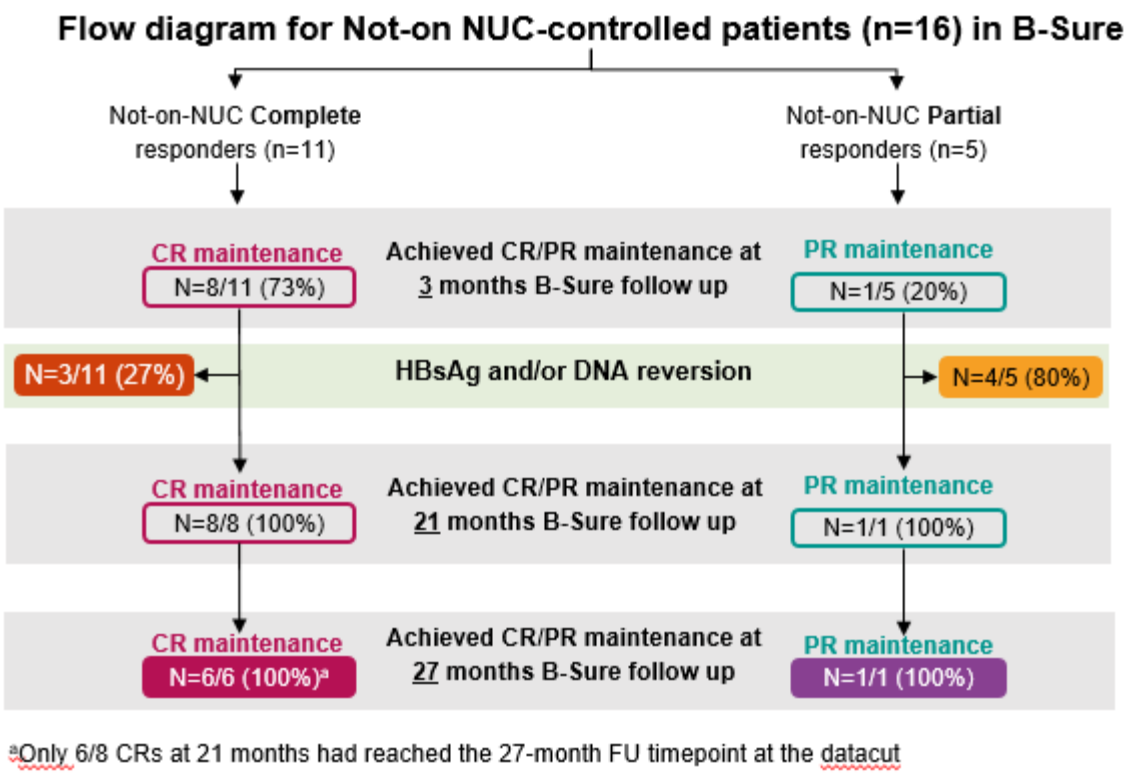
B-Together: Sequential therapy with bepirovirsen followed by pegIFN reduces relapse rate



Buti M, et al. J Hepatol 2025; 82:222-234

B-Sure : Functional cure in response to bepirovirsen in B-Clear On-NUC and Not-on-NUC responders

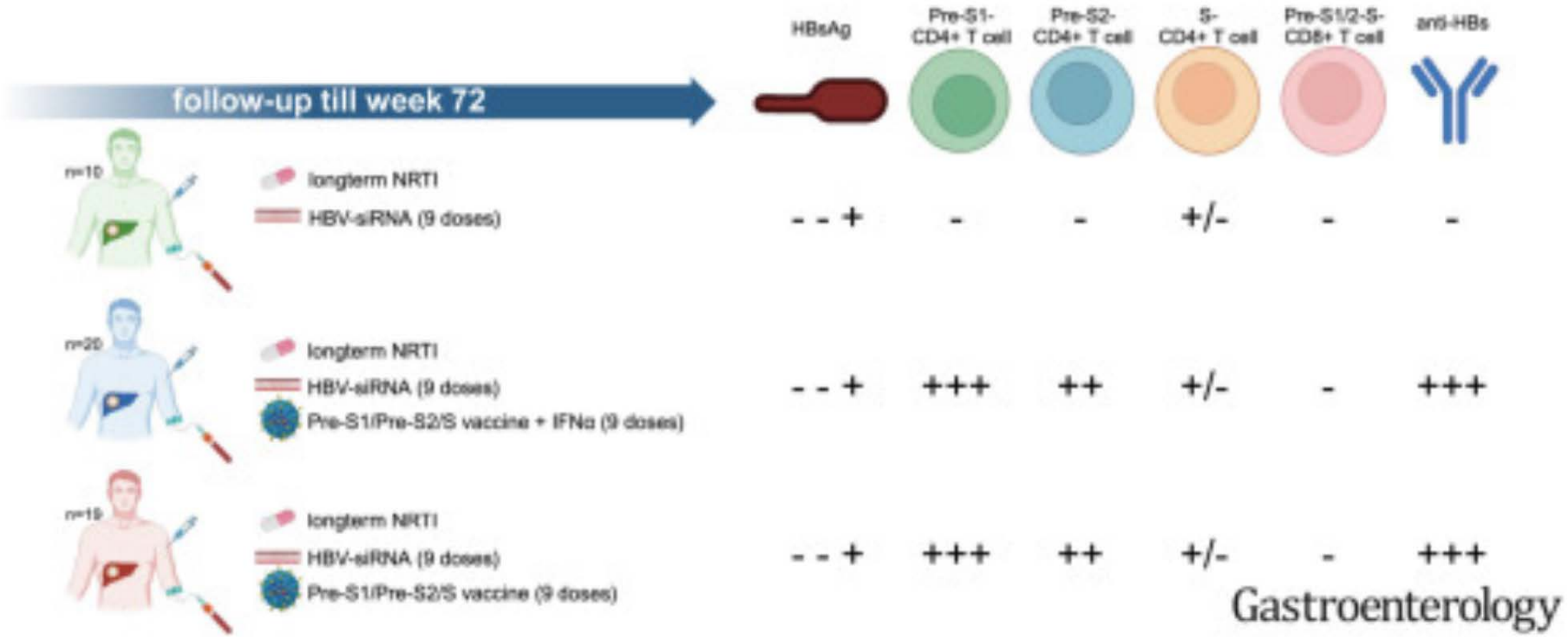




[a]Only 6/8 CRs at 21 months had reached the 27-month FU timepoint at the datacut

Walker A, et al. EASL 2025. #THU-259; Lim SG, et al. EASL 2025. #TOP-268

HBsAg by siRNA elebsiranon Vaccine (BRII-179)-Induced Hepatitis B Virus-Specific Humoral and Cellular Immune Responses



Ji Y et al Gastroenterology. 2025 Mar 3:S0016-5085(25)00466-4

El camino de la Curación de la Hepatitis B y el camino de Santiago

	Santiago	Curación
Proceso	Lleva tiempo, esfuerzo y cansancio	Prolongado que require seguimiento y compromiso
Motivación	Personal, Espiritual, …….	Mejorar y promover la salud
Apoyo	Albergues, otros peregrinos, guias	Medicamentos, personal sanitario etc….
Obstáculos	Fatiga, lesiones, condiciones climáticas	Efectos adversos, miedo, incertidumbre, estigmas

Caminado a la curacion de la Hepatitis B en 2025

1. Los Analogos de Nucleos(t)idos continúan siendo el tratamiento de primera línea para todos los pacientes

2. En un subgrupo de pacientes sin cirrosis y bajos niveles de HBsAg varias opciones

- **Discontinuación de Nucs en HBeAg negativos**
- **Interferon pegilado**
- **Nuevos Fármacos:**
  - **Bepirovirsen podria ser aprobado en el 2026**
  - **Ensayos clínicos**

“Caminante no hay camino, se hace camino al andar, golpe a golpe, verso a verso”

Antonio Machado