



Nuevas opciones terapeuticas en la hepatitis B

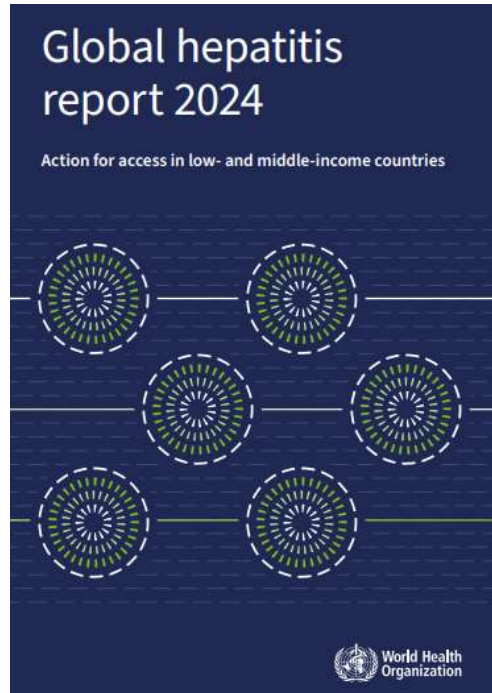
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Hepatitis B remains a global health problem



254 million people are living with hepatitis B

6.000 people are newly infected each day.



- **Despite the availability of safe and effective vaccines and treatments for 4 decades**
- **Many people remain undiagnosed in many countries,**
- **Number of people receiving treatment remains incredibly low**

Virus Hepatitis B

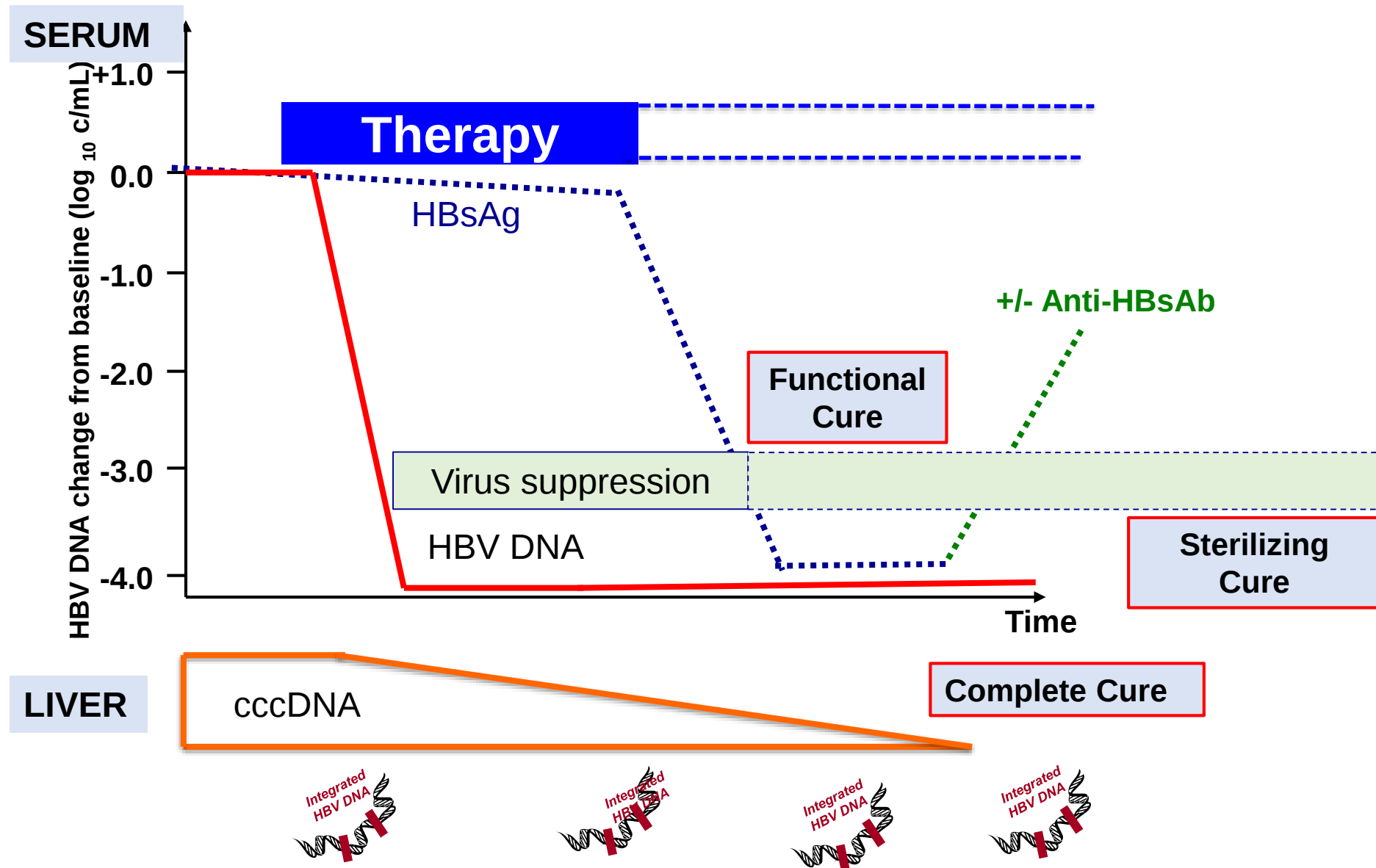
- Hepadnavirus
- virus DNA
- Pequeño, circular tamaño 3200-bp
- Partícula completa: una envoltura lipoproteica (antígeno de superficie de la hepatitis B, HBsAg) y un nucleocápside (antígeno del *core* de la hepatitis B, HBcAg). una gran cantidad de partículas incompletas (con capacidad inmunogénica pero no infecciosa) constituidas exclusivamente por HBsAg.



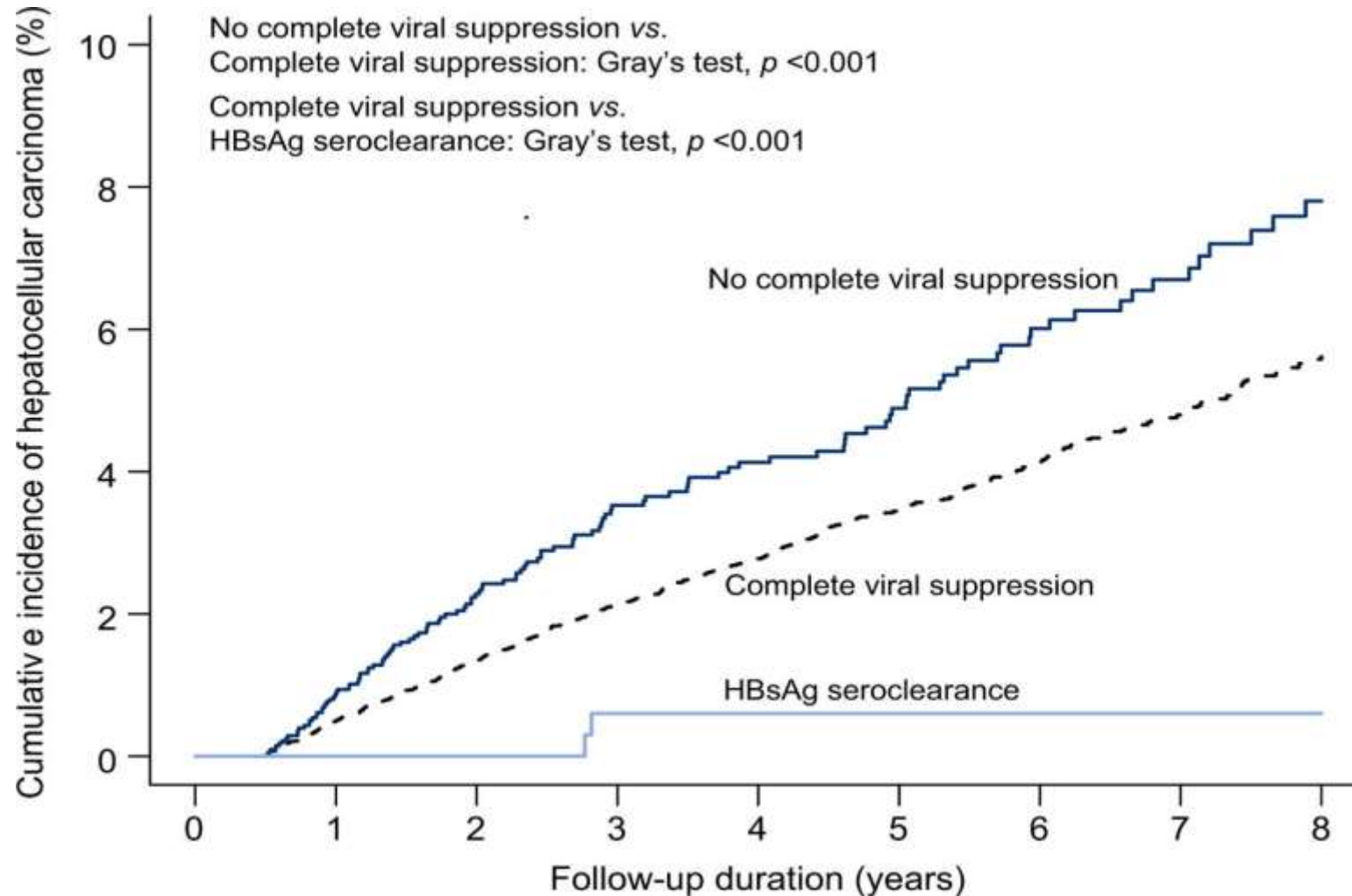
Current Hepatitis B therapy: PegIFN α or NAs

- Suppress HBV DNA replication
- Decrease liver inflammation
- Decrease the risk of cirrhosis, HCC, and liver-related death
- HBsAg loss rarely occurs, 3%–5% after 10 years of continuous NAs
- Thus, most patients require long durations or lifelong treatment prompting major efforts to develop a cure for chronic hepatitis B.

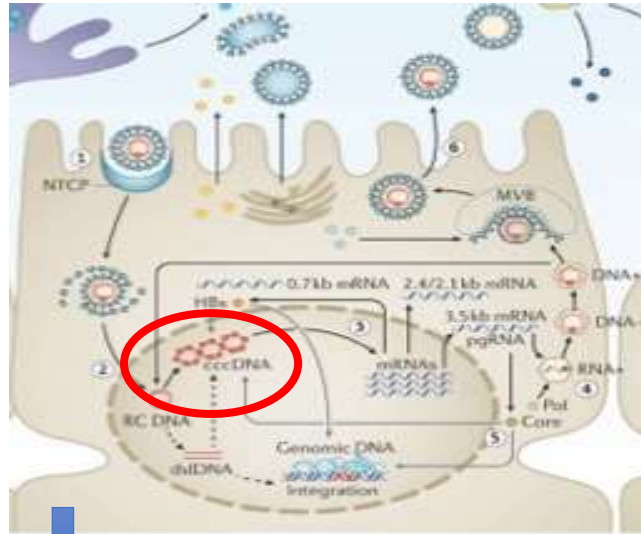
Goals of future therapies to cure HBV infections



Pérdida del HBsAg se asocia a un riesgo muy bajo de desarrollar Hepatocarcinoma



Barriers to eradicating HBV



cccDNA reservoir

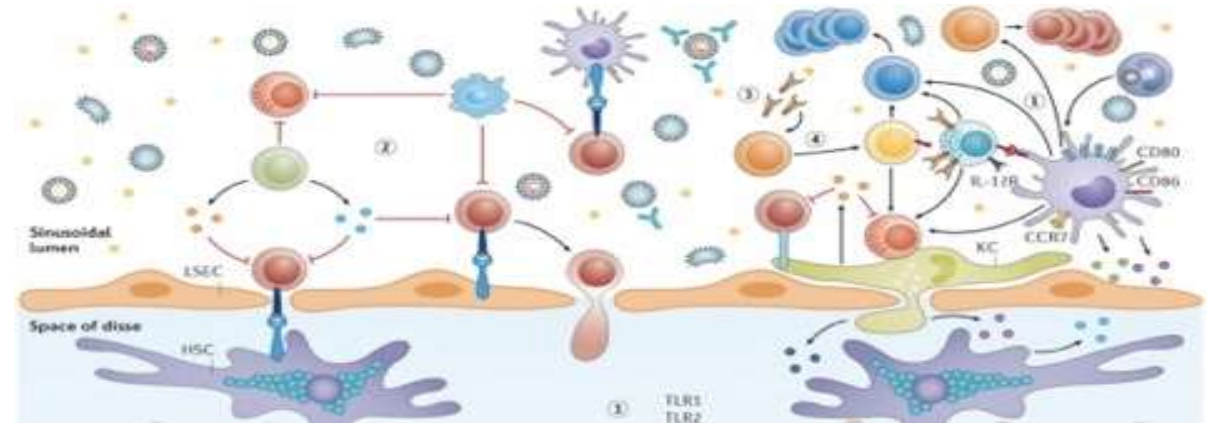
Long t_{1/2}

Continuous replenishment

Not affected by NAs and IFN

Integrated forms

HBV persistence

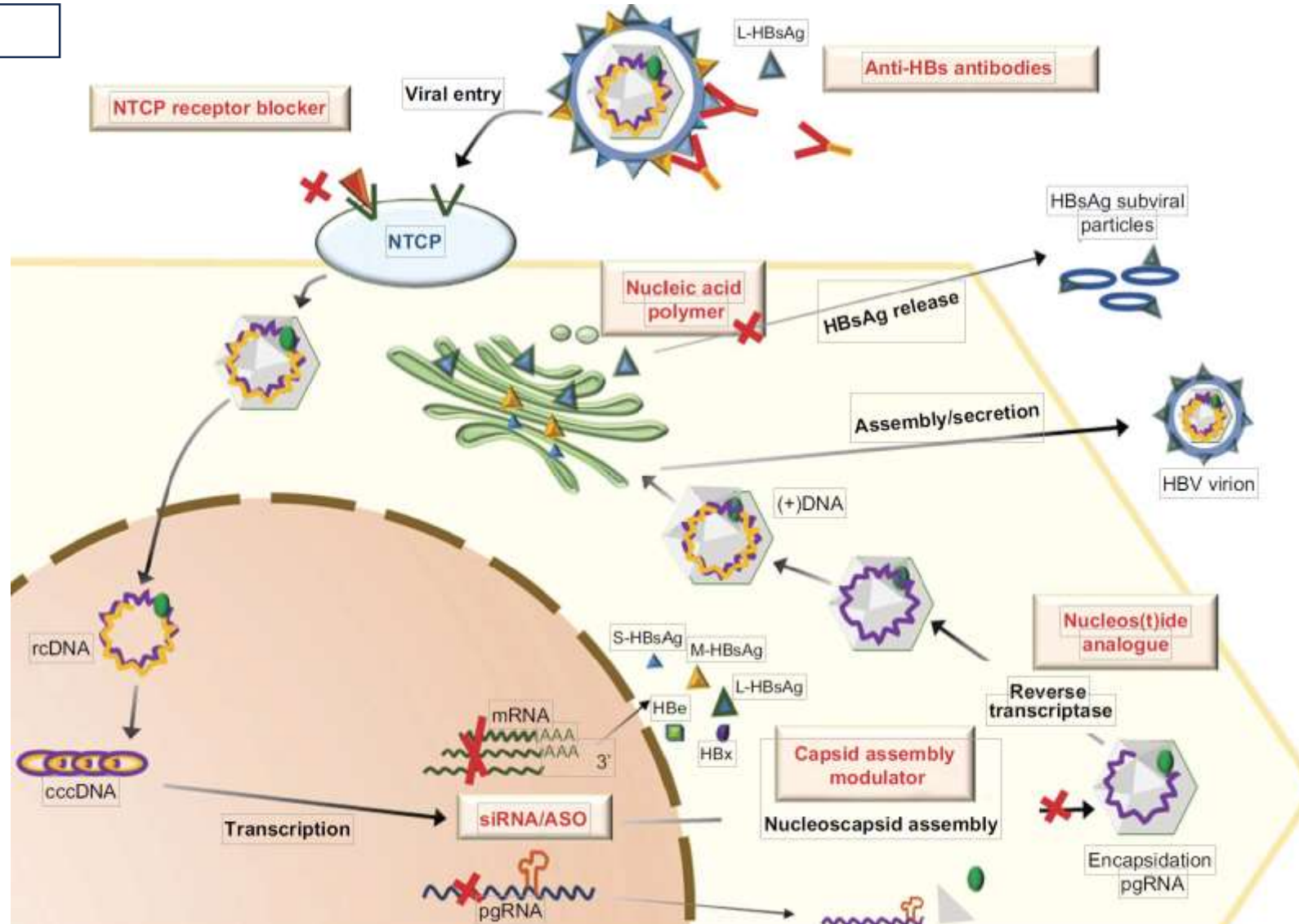


Defective CD8+ responses

Defective B cell responses

Inefficient innate response

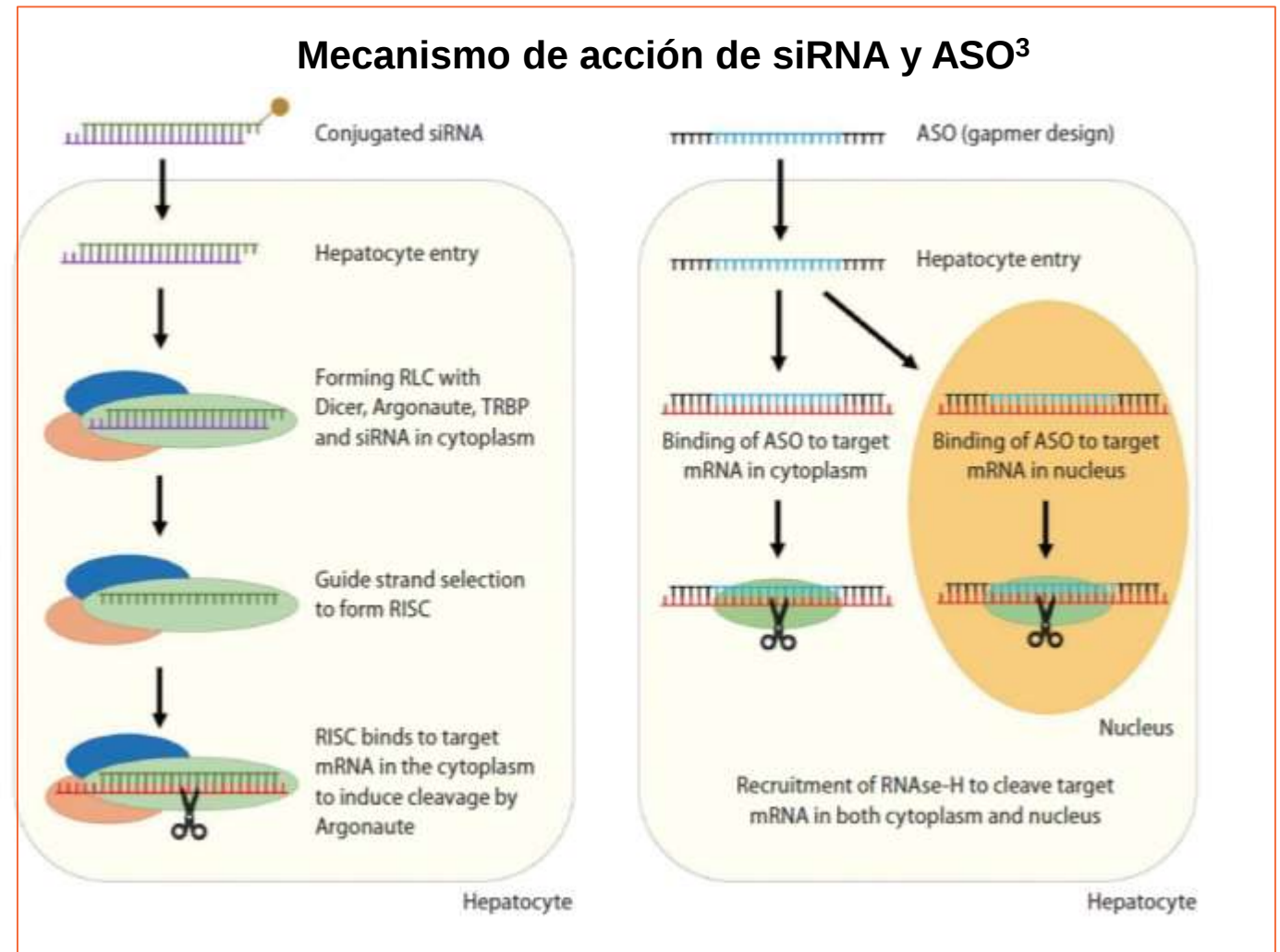
Defective immune responses



¿Cómo reducir las proteínas del VHB?

RNA de interferencia (siRNA) y Oligonucleótidos antisentido (ASO)

- Los siRNA y los ASOs tienen como diana los ARN-VHB con los objetivos¹⁻³
 - **Inhibir la replicación del VHB** (mediante la degradación del ARN pregenómico)
 - **Degradar todos los ARN-VHB** para inhibir la producción de las proteínas virales
 - La diana clave es la inhibición del **HBsAg** lo que permitiría lograr la curación funcional^{2,3}



JNJ-73763989 and bersacapavir treatment in NAs suppressed patients with chronic hepatitis B: REEF-2



Active treatment group:
JNJ-3989 (200 mg SC Q4W) +
JNJ-6379 (250 mg PO QD) + NA
N = 85

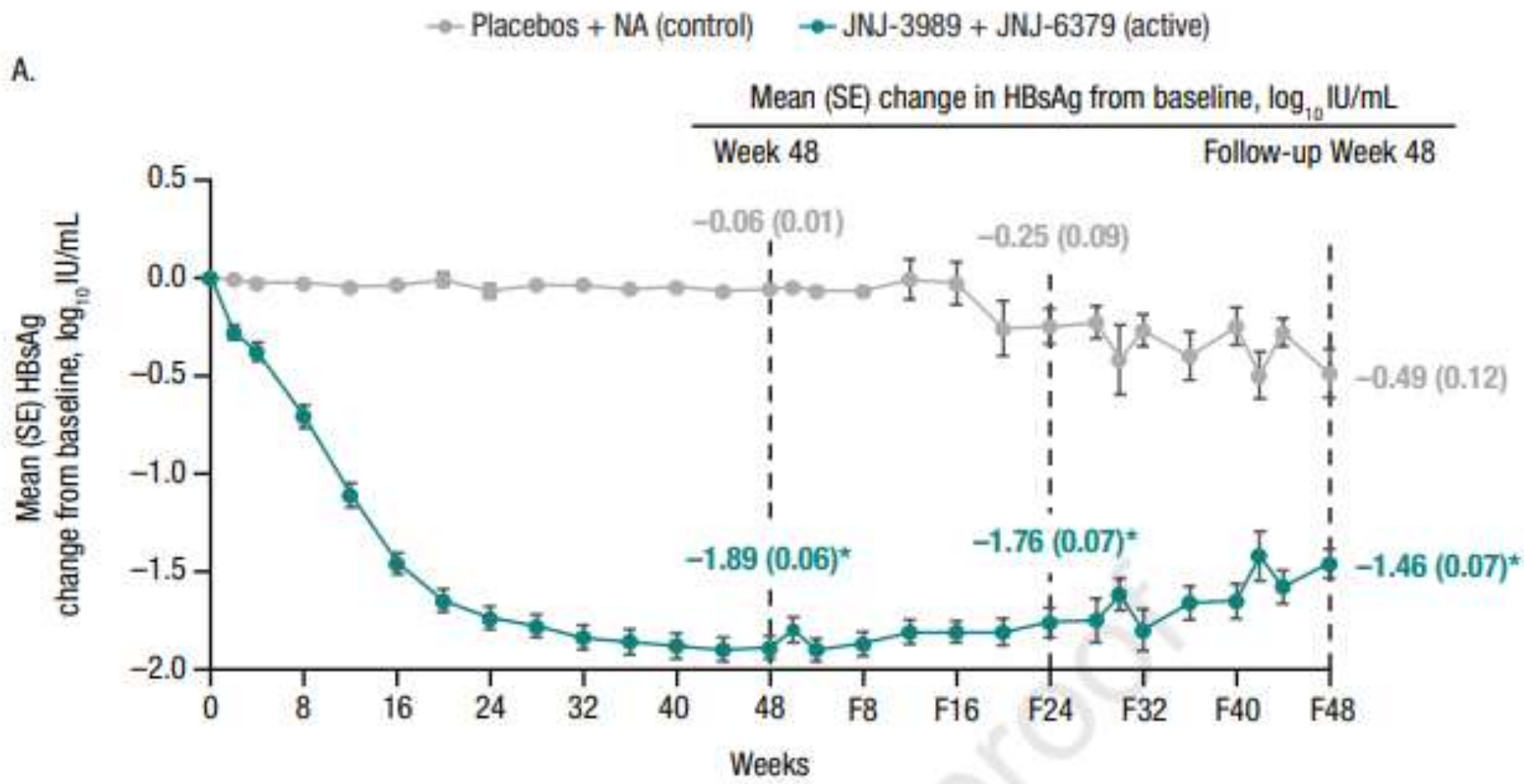
CHB diagnosis
NA suppressed
HBeAg–

Control group:
JNJ-3989 placebo +
JNJ-6379 placebo + NA
N = 45

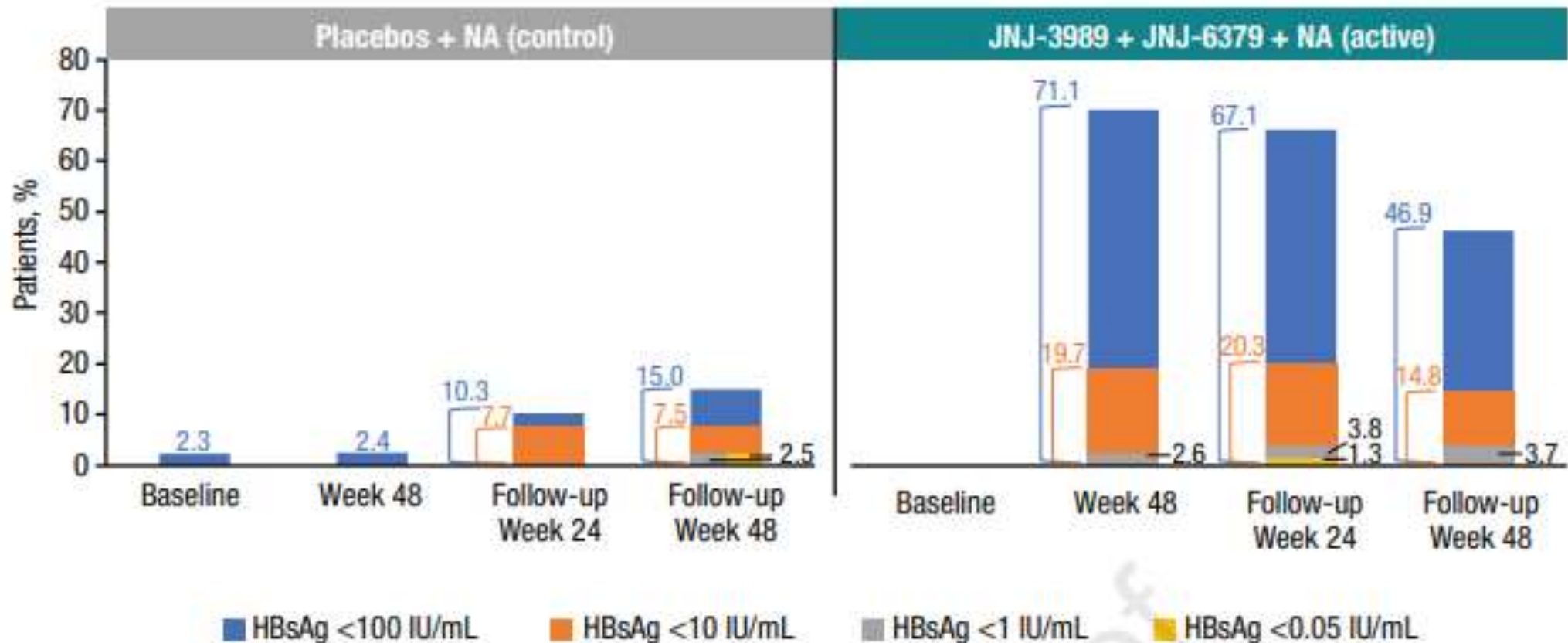
Results

- Mean HBsAg decline = $-1.89 \log_{10}$ IU/mL 15.6% had HBV DNA <LLOQ and HBsAg <100 IU/mL (partial cure)	Week 48 (end of all treatment)	- Mean HBsAg decline = $-0.06 \log_{10}$ IU/mL 0 had HBV DNA <LLOQ and HBsAg <100 IU/mL (partial cure)
No functional cure (primary endpoint)	Follow-up Week 24	No functional cure (primary endpoint)
- No functional cure 81.5% had HBsAg reductions from baseline $>1 \log_{10}$ IU/mL 46.9% had HBsAg <100 IU/mL - Lower frequency of HBV DNA relapse and ALT increases 9.1% restarted NA	Follow-up Week 48 (end of study)	- No functional cure 12.5% had HBsAg reductions from baseline $>1 \log_{10}$ IU/mL 15.0% had HBsAg <100 IU/mL - Higher frequency of HBV DNA relapse and ALT increases 26.8% restarted NA

JNJ-73763989 and bersacapavir treatment in NAs suppressed patients with chronic hepatitis B: REEF-2



JNJ-73763989 and bersacapavir treatment in NAs suppressed patients with chronic hepatitis B: REEF-2

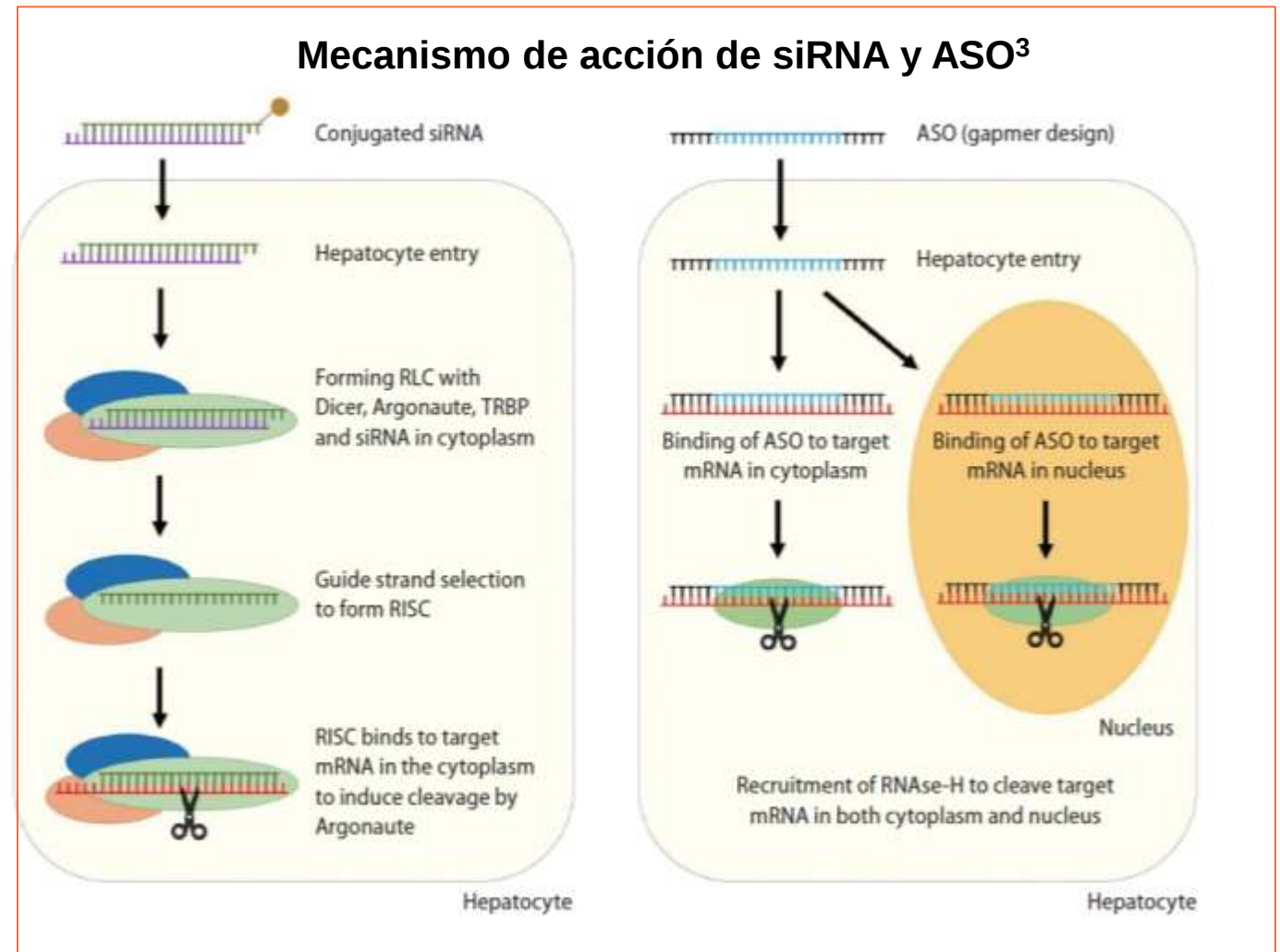


Al final trata 71% tenia niveles de HBsAg inferior a 100 UI/mL

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Study design



Inclusion criteria

- Chronic HBV infection ≥ 6 months
- ALT $\leq 2 \times$ ULN
- HBV DNA < 90 IU/mL
- HBsAg > 100 IU/mL



Stratification

- HBeAg positive/negative
- HBsAg $\leq 3 \log_{10}$ IU/mL or $> 3 \log_{10}$ IU/mL



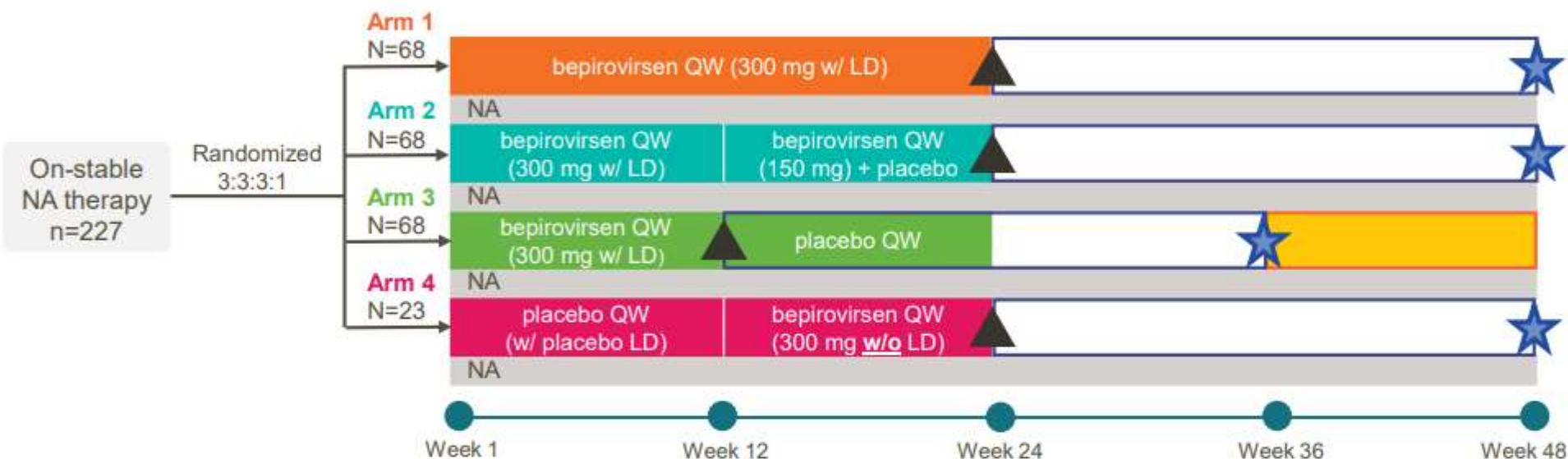
Primary endpoint analysis



Additional follow-up period



End of treatment



Primary endpoint (★): HBsAg $< \text{LLOD}$ (0.05 IU/mL) and HBV DNA $< \text{LLOQ}$ (20 IU/mL) sustained for 24 weeks from planned end of bepirovirsen treatment in the absence of newly initiated antiviral treatment.

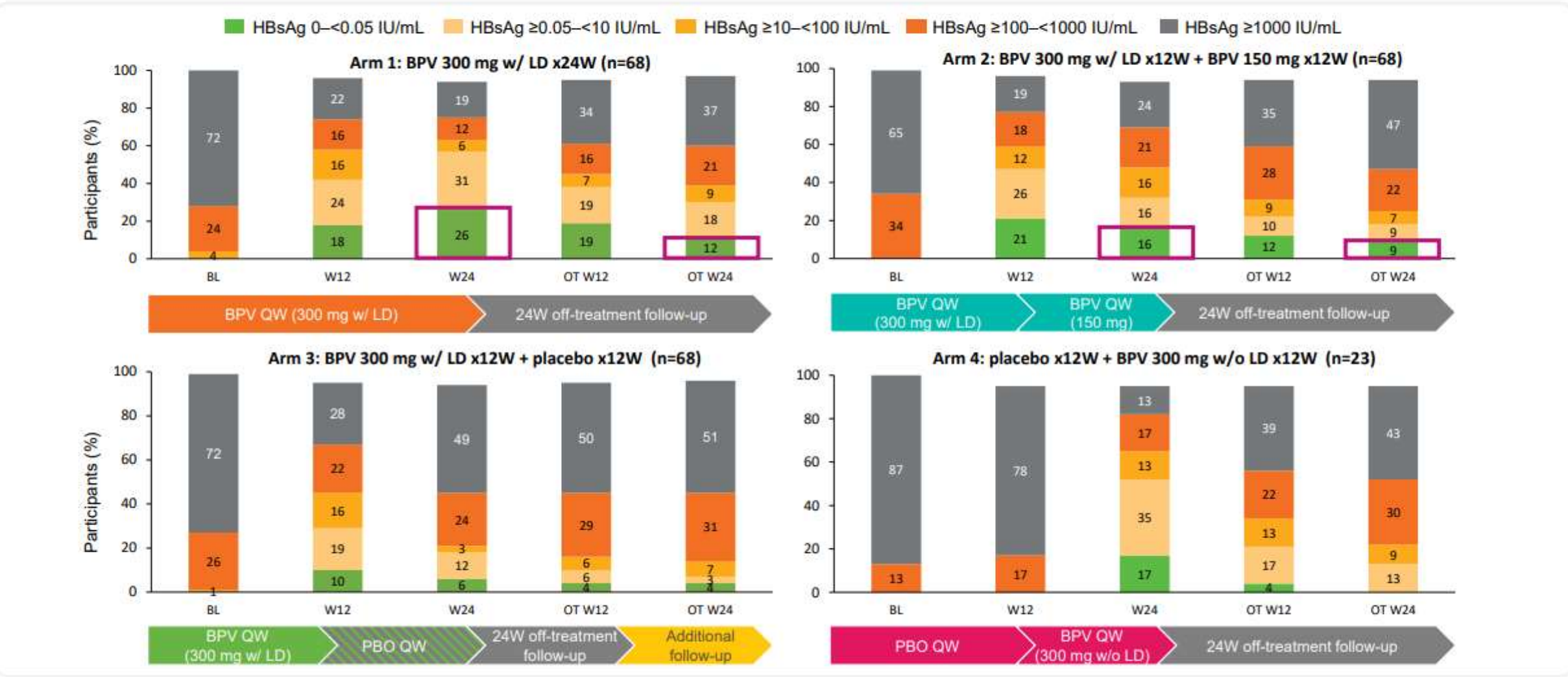
Note: Participants on stable NA therapy were expected to continue NA therapy during the study.

Doses were administered once weekly as two subcutaneous injections (two syringes total; each syringe contained either bepirovirsen 150 mg or placebo). The loading doses (bepirovirsen 300 mg [Arm 1–3] or placebo [Arm 4]) were administered on Days 4 and 11.

ALT, alanine aminotransferase; DNA, deoxyribonucleic acid; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LD, loading dose; LLOD, lower limit of detection; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogues; w/, with; w/o, without; QW, once a week; ULN, upper limit of normal.

Approximately half of participants who achieved HBsAg loss after 24 weeks of treatment (Arms 1 and 2) maintained this loss at 24 weeks post end of treatment

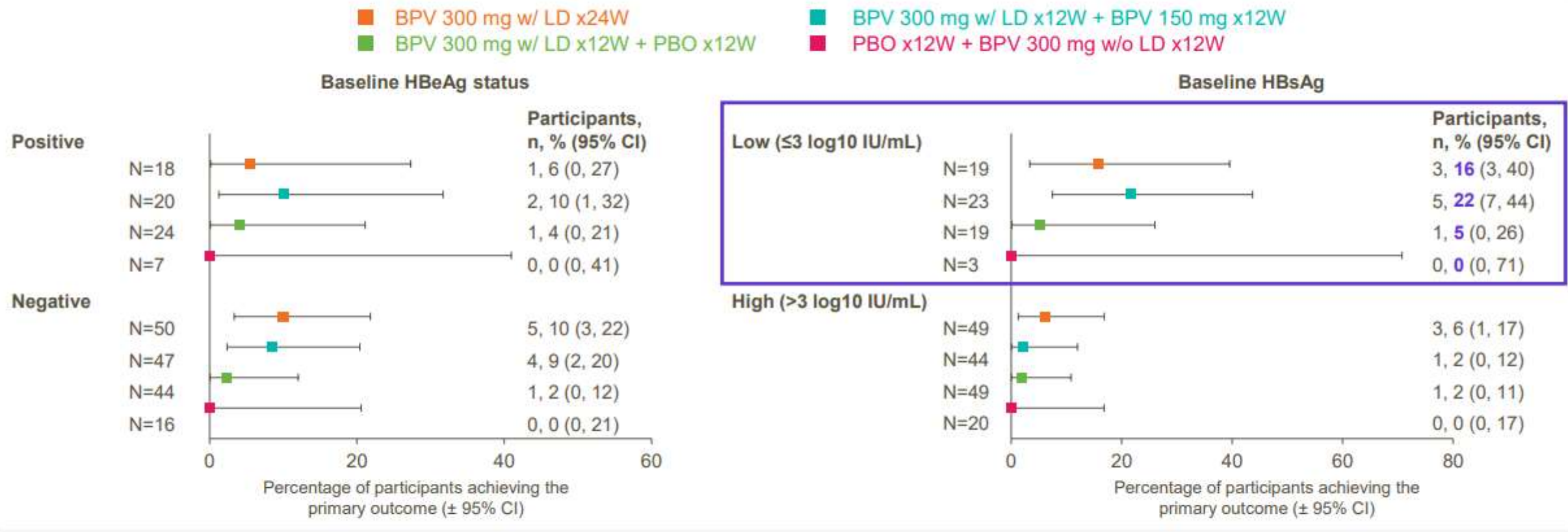
ITT population



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.

The proportion of participants with HBsAg and HBV DNA loss at end of study was higher in the low baseline HBsAg subgroup

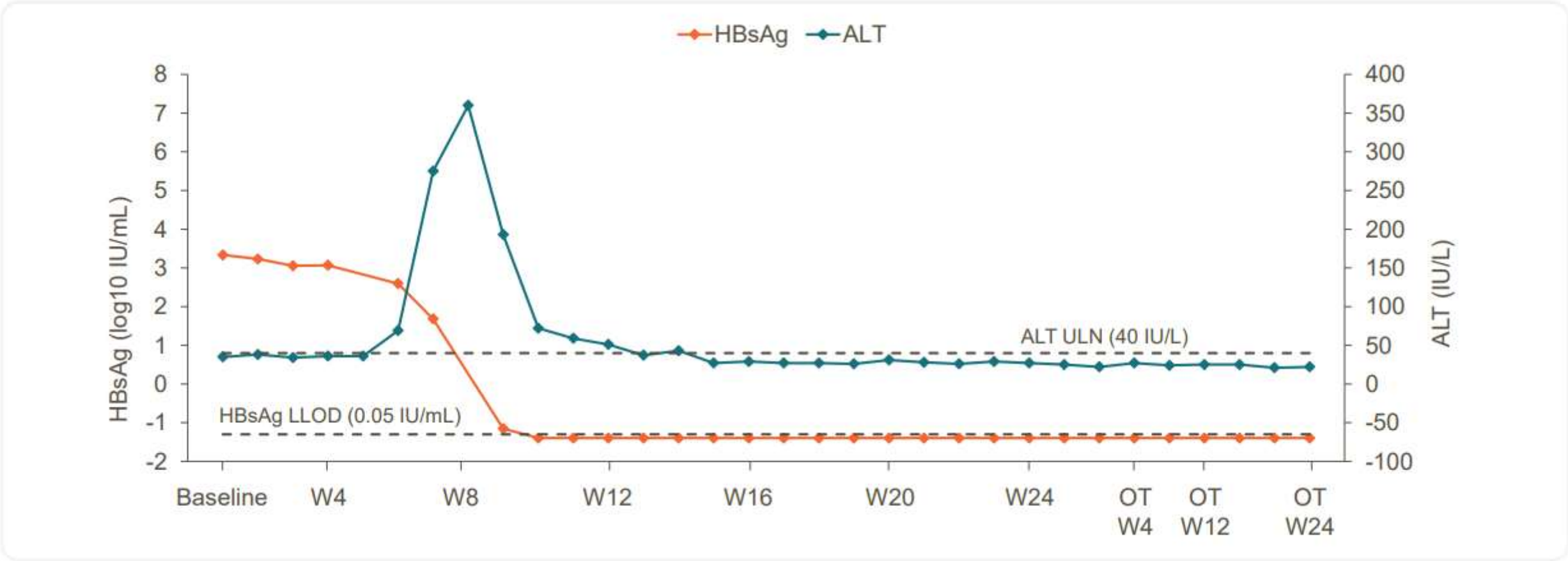
ITT population



Primary outcome was achieved in a similar proportion of HBeAg negative and positive participants (Arm 1: 10% vs 6%).

Primary outcome: HBsAg <LOD and HBV DNA <LLOQ maintained for 24 weeks post bepirovirsen end of treatment in the absence of newly initiated antiviral treatment. BPV, bepirovirsen; CI, confidence interval; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; ITT, intent-to-treat; LD, loading dose; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogues; PBO, placebo; W, week; w/=with; w/o=without.

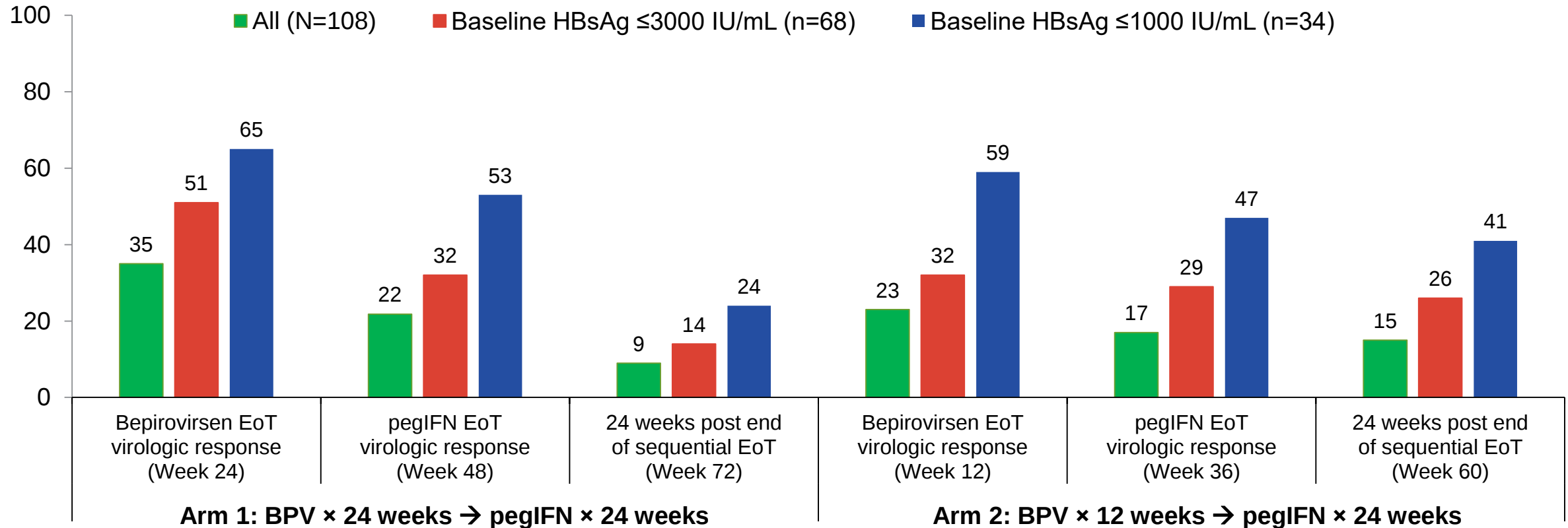
Most ALT elevations occurred in association with HBsAg decline



39 participants had ALT increase $\geq 3 \times$ ULN; most (97%) elevations occurred in association with HBsAg decline (>0.4 log from baseline).

B-Together: Tratamiento secuencial con ASO y IFN en pacientes con Hepatitis crónica B virológicamente suprimidos (NUCs)

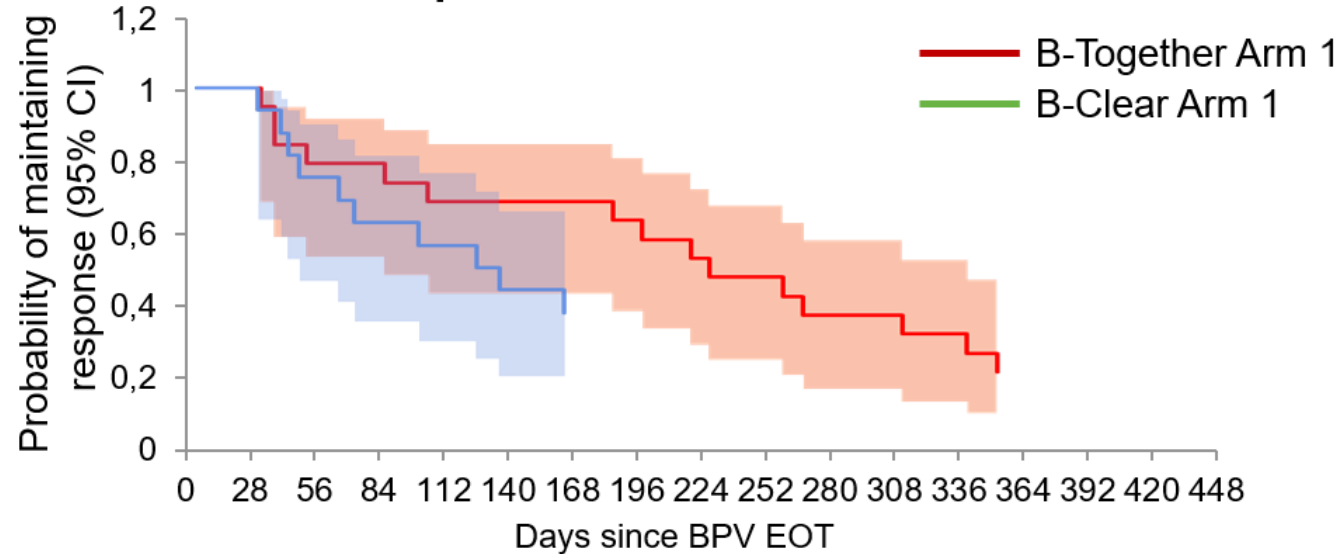
HBsAg and DNA <LLOQ



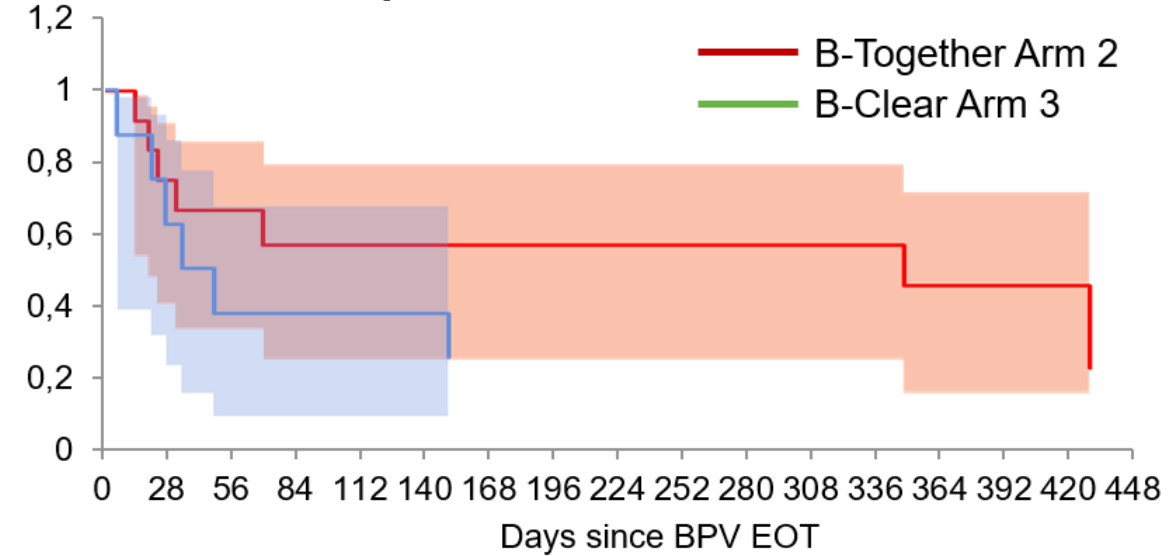
- Los niveles bajos de HBsAg fueron el único predictor de respuesta en todos los puntos ($P < 0.0001$)
- 9/55 pacientes en el brazo 1 perdieron al menos 3 semanas de pegIFN debido a las restricciones del COVID

El tratamiento secuencial ASO y PegIFN disminuye la tasa de recaídas al comparado con solo la administración de ASO

Relapses after 24 weeks of BPV



Relapses after 12 weeks of BPV



- Las tasas de recaída observadas en B-Together fueron inferiores a las de B-Clear.
- Los respondedores al final del tratamiento con BPV, el 58% de los de ambos brazos no recayeron durante el tratamiento con pegIFN.
- En los pacientes que respondieron al final del pegIFN, el 58% (brazo 1) y el 0% (brazo 2) recayeron tras interrumpir el PegIFN.
- Solo dos de los respondedores parciales al final del tratamiento con BPV respondieron durante el tratamiento con pegIFN

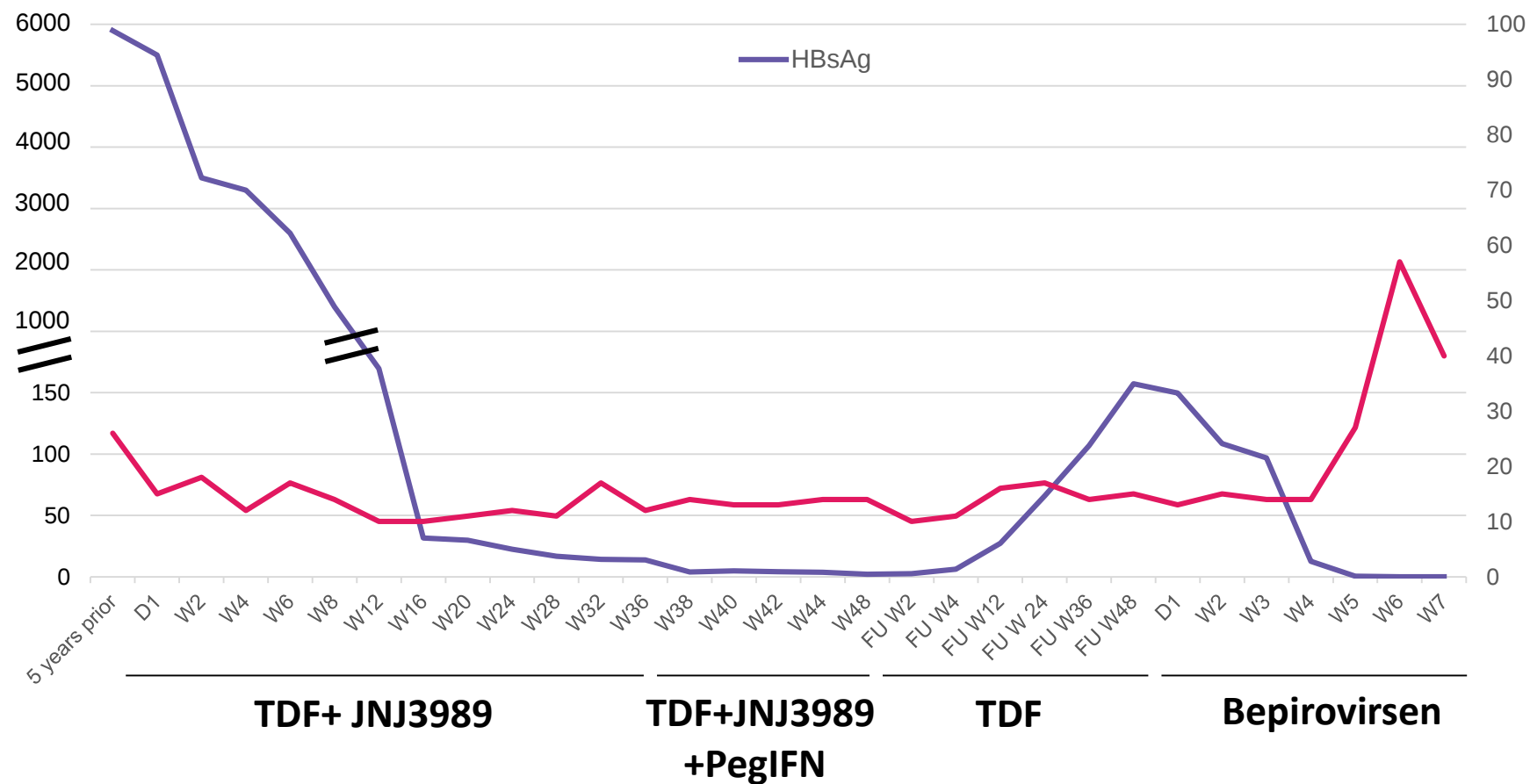
La seguridad y la eficacia de los ASO se están evaluando en un ensayo en fase III

- Se están realizando ensayos clínicos de Fase III (B-Well 1 & 2) para evaluar la seguridad y la eficacia de los ASO en monoterapia¹⁻⁶
 - En un Ensayo Clínico de fase IIb, el aclaramiento del HBsAg fue superior en los participantes con un HBsAg basal más bajo <3000 UI/ml⁷
- Ensayos clínicos en curso también están investigando la idoneidad de los ASO como tratamiento de base y si la combinación con otros MoA puede aumentar la probabilidad de aclaramiento del HBsAg⁸⁻¹⁰

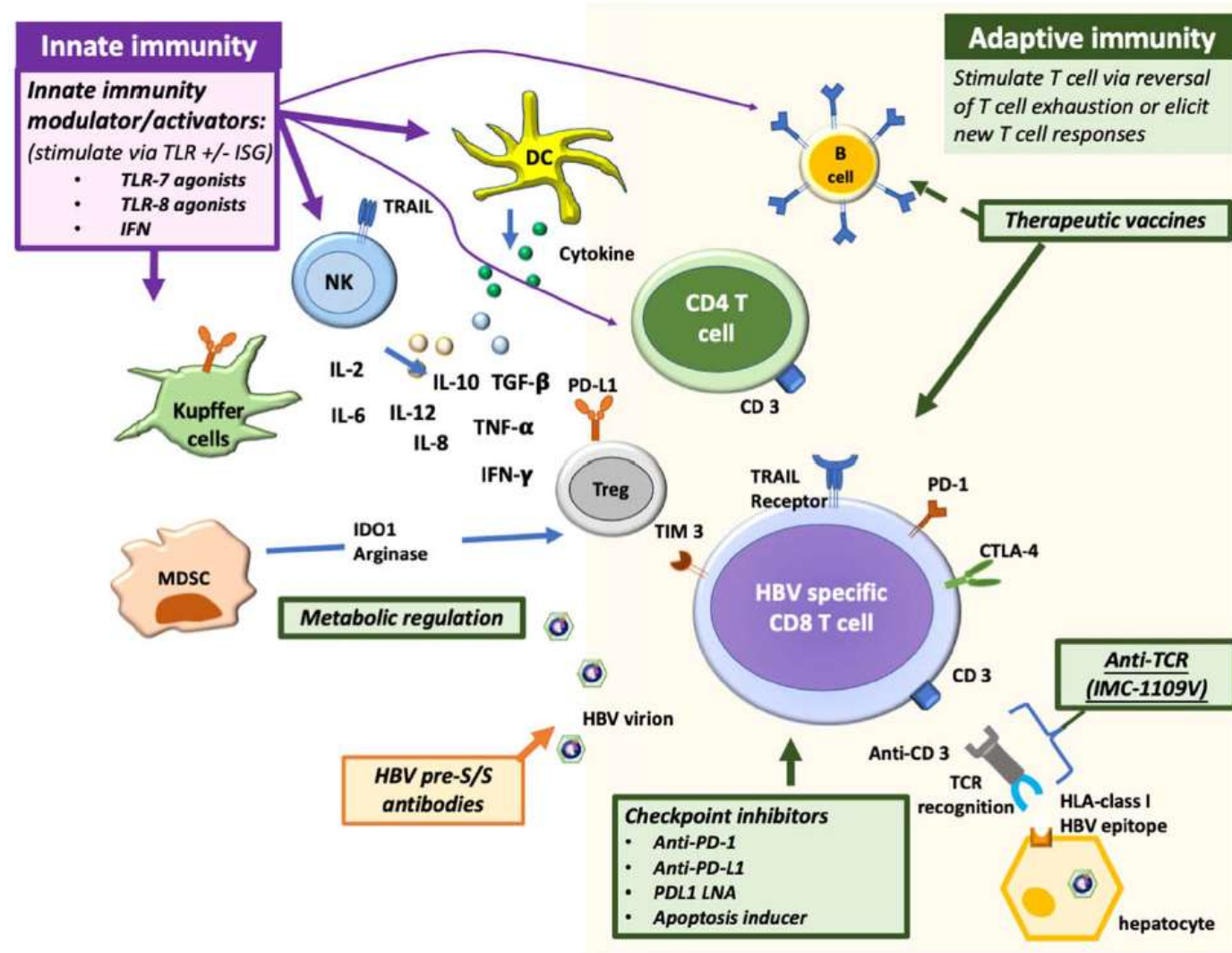
ASO: oligonucleótido antisentido; HBsAg: antígeno de superficie de la hepatitis B; MoA: mecanismo de acción

1. ClinicalTrials.Gov. NCT05630807. Available at: <https://clinicaltrials.gov/ct2/show/NCT05630807>; 2. ClinicalTrials.Gov. NCT05630820. Available at: <https://clinicaltrials.gov/ct2/show/NCT05630820>; 3. ClinicalTrials.Gov. NCT04449029. Available at: <https://www.clinicaltrials.gov/ct2/show/NCT04449029>; 4. ClinicalTrials.Gov. NCT05717686. Available at: <https://clinicaltrials.gov/ct2/show/NCT05717686>; 5. ClinicalTrials.Gov. NCT04544956. Available at: <https://clinicaltrials.gov/ct2/show/NCT04544956>; 6. ClinicalTrials.Gov. NCT04971928. Available at: <https://clinicaltrials.gov/ct2/show/NCT04971928>; 7. Yuen MF et al. *N Eng J Med* 2022;387:1957–68. 8. ClinicalTrials.Gov. NCT04676724. Available at: <https://www.clinicaltrials.gov/ct2/show/NCT04676724>; 9. ClinicalTrials.Gov. NCT05330455. Available at: <https://www.clinicaltrials.gov/ct2/show/NCT05330455>; 10. ClinicalTrials.Gov. NCT05276297. Available at: <https://clinicaltrials.gov/ct2/show/NCT05276297>.

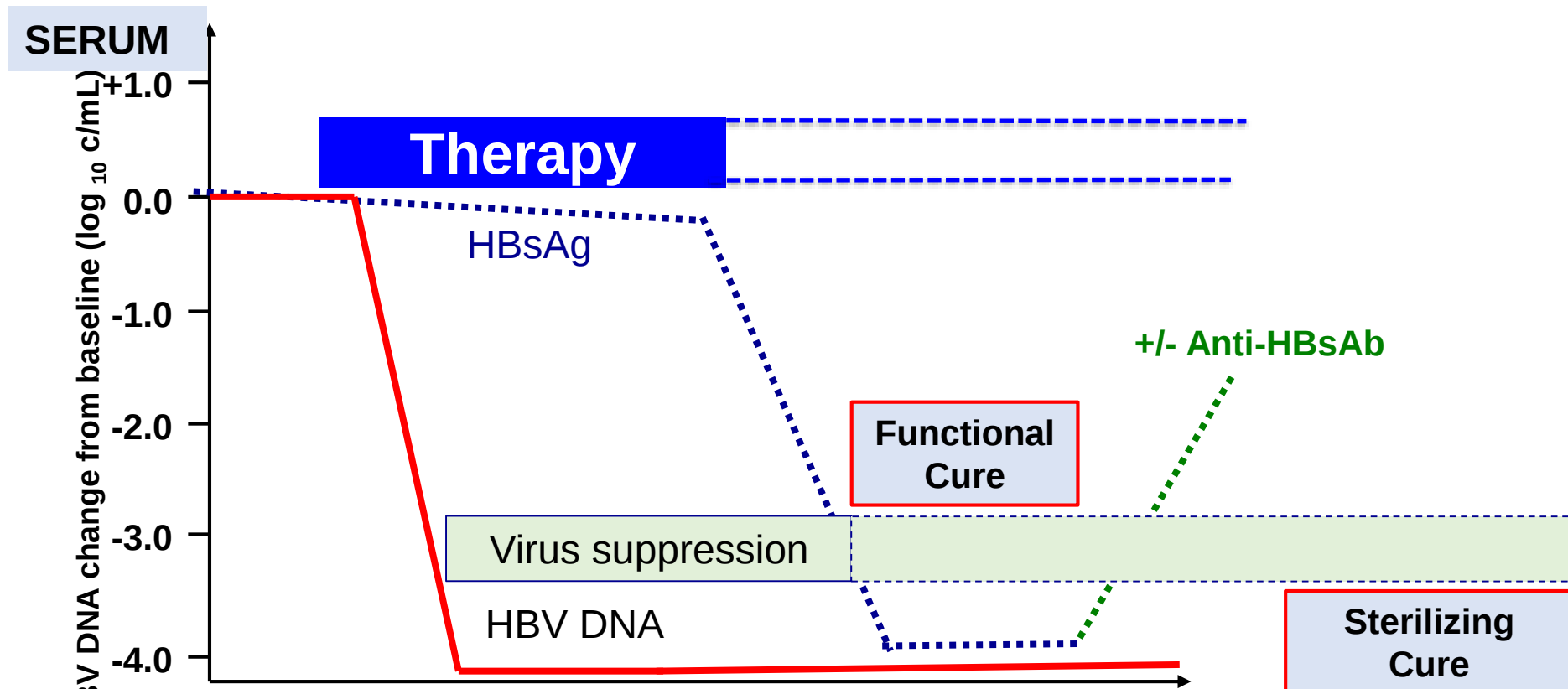
Female, 57 years, Chronic Hepatitis B HBeAg negative



Immunomodulatory therapies aimed to restore innate and adaptive immune responses against HBV



Goals of future therapies to cure HBV infections



2022 AASLD-EASL HBV-HDV Treatment Endpoints Conference

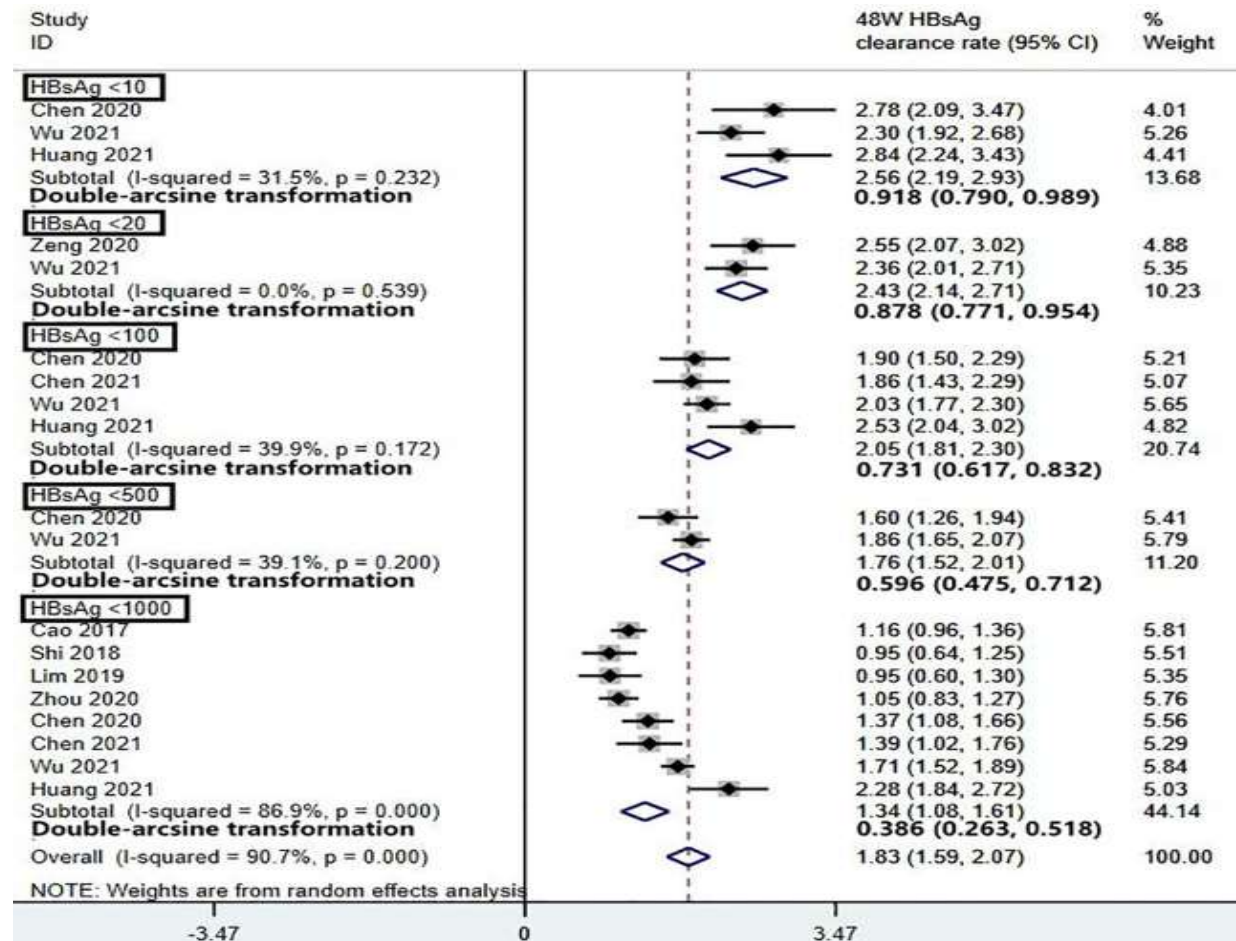
Estrategia Alternativa

HBsAg <100 IU/mL y ADN-VHB < LLOQ 24 semanas post-trat

Los niveles basales de qHBsAg predicen la pérdida del HBsAg en portadores inactivos del VHB tratados con peg-IFN

Meta-análisis de 11 estudios con 1026 pacientes

Tasa de aclaramiento del HBsAg[†]



92 % (IC del 95 %: 79 %-99 %)

88 % (IC del 95 %: 77 %-95 %)

73 % (IC del 95 %: 62 %-83 %)

60 % (IC del 95 %: 48 %-71 %)

39 % (IC del 95 %: 26 %-52 %)

Strategies for HBV Cure



- NA
- Entry inhibitors
- CAMs
- siRNAs/ASOs

Replication inhibition

Which direct-acting antiviral to combine with NA?

- siRNA/ASO
- NAP/STOP
- Gene editing
- Epigenetic modifications

Decrease viral antigen production / release

How to eliminate or silence integrated HBV DNA transcription?

- TLR7/8 agonists
- Anti-PD1/anti-PDL1
- B/T cell vaccines
- IFN
- Pre-S/S antibodies

Enhance or restore innate/adaptive immune responses to HBV

How to characterize immune phenotype of patient and select most effective immune modulatory therapy?

Functional cure

Sustained HBsAg loss and undetectable HBV DNA after finite course of treatment

Is functional HBV cure as currently defined feasible?
What would it take to achieve that goal?

Resumen

- Las tasas de curación funcional con los tratamientos actuales como los NA¹son muy **bajas**.
- Los siRNA, y ASO consiguen con una **reducción importante** en los niveles de HBsAg²⁻⁵.
 - Se necesitan más datos **a largo plazo** para conocer si esta respuesta es persistente⁴.
- Las células del SI pueden mostrar un fenotipo agotado con altas cargas de antígeno o ADN viral; por lo que estimular el **sistema inmunitario** podría ayudar a lograr la curación funcional⁵.
- Se necesitan más estudios para identificar combinaciones de moléculas que reduzcan los niveles de HBsAg y estimulen el sistema inmune para lograr la cura funcional⁶⁻⁷.

ASO: oligonucleótido antisentido; NA: análogo de nucleós(t)idos; NAP: polímero de ácidos nucleicos; siRNA: ARN pequeño de interferencia

1. Hirode G et al. *Gastroenterology* 2022;162:775–771.e4; 2. Blanchet M et al. *Antiviral Res* 2019;164:97–105; 3. Yuen M-F et al. *N Engl J Med* 2022;387:1957–1968;

4. Hui RW-H et al. *Clin Mol Hepatol* 2022;28:408–424; 5. Lim SG et al. *Nat Rev Gastroenterol Hepatol* 2023;20:238–253; 6. Wong GLH et al. *J Hepatol* 2022;76:1249–1262;

7. Michler T et al. *Gastroenterology* 2020;158:1762–1775.e9